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THERAPY FOR CARCINOMA OF THE UTERINE CERVIX; PART I: IRRADIATION

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RECENT enthusiasm for the surgical treatment of carcinoma of the uterine cervix has resulted in a tendency to forget the continuing place of irradiation for cure or for palliation, and sometimes as a complement to surgical therapy. This report presents our current use of irradiation in the treatment of cervical carcinoma. A second communication will present the indications for surgery for this condition.

General Indications for Irradiation

We do not hold to strict rules for the treatment of cervical carcinoma, beyond adhering to the concept of individualization of treatment for each patient. It is as wrong to subject all patients to irradiation as it is to subject all to surgery. The individually appropriate therapy involves consideration of: the extent of the patient's disease, her general physical condition, her age, her marital status, and the quality of available irradiation or surgical technics.

At present we use irradiation as primary therapy for most of the League of Nations stage I and stage II uterine cervical carcinomas. An additional major indication for irradiation is advanced disease that is not amenable to surgery or

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to curative radiotherapy. Irradiation is particularly valuable in the control of potentially exsanguinating bleeding and intractable deep pelvic pain.

Pretreatment Evaluation

Uterine cervical carcinoma is more than a gynecologic disease, for it may spread to involve the rectum, the bladder, or the deep pelvic nerves. Thus, the patient may be evaluated by a urologist, a proctologist, an internist, and a neurologist, in addition to the gynecologist and the radiologist. Pretreatment laboratory studies include a urinalysis, complete blood count, and blood sugar and urea determinations. Roentgen examinations of the chest and of the urinary tract are performed. These procedures indicate the extent of the primary lesion, help to establish whether or not there is metastasis, and also furnish valuable information in regard to the pretreatment status of these systems. Roentgenograms taken before treatment are invaluable records to consult a year or two later, when it may be necessary to differentiate advancing disease from the late effects of irradiation. Such records may also be of medicolegal importance. When all of these studies are completed, a gynecologist and a radiologist consult and decide on an appropriate therapeutic approach. When indicated, either a urologist or a colon surgeon or both participate in the consultation and ultimate decision.

When irradiation is the elected treatment, the gynecologist's responsibility is not transferred to the radiologist. The patient is seen weekly during therapy so that the gynecologist may observe the patient's progress and may treat complications of irradiation. Psychological assistance to the patient is of the utmost importance, and the physician can aid the patient materially in her formulation of a proper perspective in relation to the disease.

Limitations of Irradiation

Irradiation is potentially lethal to all living tissue. Its therapeutic effectiveness lies in the difference in sensitivity between normal and neoplastic tissues. The tolerance of normal tissues is in most instances greater than that of carcinoma, but the margin of safety is not great. In spite of the reports of sensitivity-reaction and radiation-reaction determinations in assessing irradiative sensitivity, there is, at present, no generally available method for determining whether a specific tumor will or will not be sensitive to irradiation.

It has been determined by trial and error over many years that from 6,000 to 8,000 r will destroy most carcinomas originating in the uterine cervix. About 12 per cent of these tumors will be radioresistant and will not be killed by many times this number of roentgens. In view of this cancerocidal dose, our objective is to deliver a minimum of 6,000 r not only to the primary tumor, but also to the parametrium and the lymphatic drainage areas in the pelvis. In accomplishing this, the bladder, rectum, small bowel, and bones of the pelvis also are irradiated. Each of these structures can be injured permanently if care is not used in giving treatment. In order to take advantage of the more rapid recovery rate of normal tissues, irradiative therapy is administered in multiple doses over a period of

several weeks. Thus, neoplastic tissues receive a lethal dose before the normal structures do.

In the past, skin reaction has limited the amount of external irradiation that could be given, for if the dose exceeded that which produced erythema, permanent damage to the skin might result. When erythema was achieved, it was hoped that the tumor itself would have received sufficient irradiation to destroy it. Using a 250-kilovolt roentgen machine the "erythema dose" is reached at approximately 3,000 r. When this dose is given both through anterior and posterior portals, a maximum parametrial depth dose of from 2,000 to 2,500 r is attained.

Radium generally is used to supplement external irradiation, by delivering a cancerocidal dose to the primary tumor and to the tissue immediately surrounding it. Some of this irradiation reaches the lateral walls of the pelvis, but the amounts are small because of the inverse relationship between the distance and the dose. If a dose of from 6,000 to 7,000 r is delivered to the cervix, only from 2,000 to 2,500 r will reach the lateral pelvic walls. Thus, by combining the maximum dosage attained with a 250-kilovolt roentgen machine and that delivered by radium, a lethal dose can be reached at the cervix, but at the same time there is a 2,000 r deficit at the pelvic wall (Table 1). Consequently, 250-kilovolt roentgen therapy is inadequate for the control of carcinoma at the lateral wall.

Table 1.—*Comparison of radiation dosages delivered by 250-kilovolt roentgen therapy and cobalt-60 teletherapy*

Treatment		Number of roentgens delivered to	
		Paracervical tissue	Pelvic wall
250-kilovolt		2,000	2,000
Radium		6,000	2,000
	Total	8,000	4,000
Cobalt-60		4,000	4,000
Radium		6,000	2,000
	Total	10,000	6,000

Cobalt-60 (Co-60) teletherapy and 2,000,000-volt roentgen therapy have several advantages over the 250-kilovolt therapy unit. This is not due to any specific biologic effect of the shorter and more powerful rays, but is due to several physical assets inherent in the super-voltage apparatus. These are: (1) greater penetration with a consequent increase in the depth dose; (2) less back and side scatter, thereby decreasing the integral dose and radiation reactions; (3) skin-sparing effect because of the occurence of maximum ionization (which causes tissue reaction) at a level of from 4 to 5 mm. below the surface of the skin;

(4) no increased absorption of irradiation by bone; this permits the use of lateral fields. Because of these factors a lethal dose of irradiation can be administered to carcinoma at the lateral pelvic walls (Table 1).

A Method of Irradiative Therapy

Since October of 1954, we have employed cobalt-60 teletherapy instead of 250-kilovolt roentgen therapy. Four portals are used, one anterior and one posterior, each 10 cm. by 15 cm., and two lateral portals, each 10 cm. by 12 cm. Lateral fields are used to produce a more homogeneous dose to the parametrium and lateral pelvic walls. We believe that these portals are preferable to sacrosciatic or other angled fields, and we have not encountered aseptic necrosis of the head or neck of the femur as a consequence of this therapy. Rotational therapy was tried and has been discarded because it does not provide homogeneous dosage.

In planning the course of pelvic irradiation we attempt to deliver 5,000 r to the central portion of the parametrium on each side in an 18-day period. Two fields are treated each day. The anterior portal and right lateral portal are treated on one day, and the two remaining fields are treated on the following day. Treatment is given five days a week until a maximum dose of from 2,500 to 3,000 r has been delivered to the skin of each portal. The midportions of the anterior and of the posterior fields are blocked with lead after a depth dose of 1,000 r has been delivered to the cervix. This is done to decrease the irradiation to the bladder and the rectum and to avoid overtreatment of the cervix and nearby tissues.

The above dose does not result in any skin reaction. There may be diarrhea in the first week of therapy but this rapidly disappears when the lead block is applied. There have been no delayed effects either on the small or on the large bowel.

In addition to the cobalt-60 teletherapy, radium is applied either before or after the external therapy, the sequence depending sometimes on anatomic considerations and sometimes on convenience. It is desirable to have a variety of radium applicators available in order that treatment can be individualized according to the anatomic variations occasioned by the disease. We have used the London type of ovoids together with a tandem, the Ernst applicator, the Silverstone colpostat, and low-intensity radium needles. Radium applications are made by a gynecologist with a radiologist in attendance in order that the technical skills of both specialists may be utilized.

When the Ernst, the modified London, or the Silverstone applicator is used, the radium is left in place for about 72 hours, and from 5,500 to 6,000 mg.-hours of irradiation is given. An average of 6,000 gamma roentgens is thereby delivered to point A, which is 2 cm. lateral to the cervix, and 2 cm. above the vaginal vault. When low-intensity radium needles are used, the dosage is varied in accordance with the number of needles used and the distribution of radium.

Radium treatment presents the greatest risk to the bladder and the rectum, and it is for this reason that the radium is carefully positioned under optimal conditions of relaxation obtained by general anesthesia. Adequate packing is employed to separate these structures as far as possible from irradiation sources, and the patient is confined to bed. In spite of all precautions, irradiation cystitis and proctitis do occur occasionally, but we believe that these sequelae constitute a justifiable risk of irradiation and are not completely avoidable.

Irradiation for Palliation

External irradiation may also be used for palliative purposes in treating persistent disease manifested by potentially exsanguinating vaginal bleeding or by leg and pelvic pain requiring narcotics. In many instances when patients have had previous external irradiation with 250-kilovolt equipment, the abdominal skin is so scarred and thickened that it is not wise to deliver further treatment by this method. In those cases, Co-60 teletherapy can be used in either of two ways. On some occasions total pelvic irradiation is used through conventional portals with dosages limited to from 2,000 to 3,500 r to the pelvic wall. In others, a single portal is treated in order to reach the source of pain or bleeding; treatment is administered to the extent of the desired therapeutic effect, but not in excess of 3,500 r. The use of Co-60 teletherapy may obviate the need for cordotomy with its not infrequent undesirable side effects.

Posttreatment Follow-Up

It is too early to evaluate the over-all effectiveness of Co-60 teletherapy, yet we have noted the advantages outlined above. With more radical forms of surgical therapy now generally available, close follow-up study is indicated so that those patients who have radioresistant lesions may be offered further treatment. Since a homogeneous dosage of irradiation is given throughout the pelvis, it is now possible to follow patients with greater assurance, since if the primary tumor is controlled, the tumor in the lateral pelvis generally will be controlled. It is our practice to see patients six weeks after the completion of therapy, every three months for the first year, every six months for the next four years, and then at yearly intervals. Our follow-up examinations include not only the standard pelvic examination but also routine cervical cytologic studies and, when indicated, roentgen studies of the urinary tract, cystoscopy, and proctoscopy.

Summary

Irradiative therapy is an important method of treatment of cervical carcinoma at the Cleveland Clinic, and the use of cobalt-60 teletherapy has made more intense and homogeneous therapy possible. The treatment of any cervical carcinoma should be individualized. An integrated approach through use of various medical and surgical specialties is presented.

REPAIR OF INJURY TO THE COMMON BILE DUCT

Results in 69 Cases

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THIS report is based on a survey of the results of 69 operations for repair of injuries to the common bile duct. The operations were performed at the Cleveland Clinic Hospital during the 15-year period from 1940 to 1955 and included hepaticoduodenostomy as well as more complicated procedures.

There is little agreement among surgeons as to which technic of reconstruction of the common bile duct provides the best results. Cole and associates[1,2] advocate the use of Roux-Y procedures, which they expect to produce good results in 90 per cent of the cases if from 2 to 3 cm. of duct is available for anastomosis, and if the surgeon himself is "satisfied" with the operation. However, if the proximal stump of the duct is short, Cole believes that only about 65 per cent of the results will be good. In Cole's cases the over-all results of hepaticojejunostomy, including those operations in which the surgeon himself was "not satisfied" at the end of the procedure, were satisfactory in 79 per cent of the cases. Ravdin[3] believes that an end-to-end anastomosis should be made. Aust and Varco,[4] reported that in their series of 70 adult patients, surgical results were satisfactory in 48 patients. Best results (satisfactory in 9 of 10) were obtained with hepaticojejunostomy.

Walters[5] states that for repair of injury to the common bile duct, hepaticoduodenostomy has been the most effective procedure at the Mayo Clinic. Boren and Walters[6] reported that of 147 patients who underwent hepaticoduodenostomies in the last 30 years, 96 (65 per cent) are well. In commenting on their results, Walters[7] cited the experimental work of Musgrove, Grindlay, and Karlson who reported that in dogs, postoperative cholangitis resulted from stricture rather than from reflux. He[7] also mentioned that Klement and Lie had better results with hepaticoduodenostomy than with Roux-Y procedures. McGoon and Claggett[8] report that of 52 patients who received prostheses of Vitallium, 16 patients have satisfactory results. In an additional 13 patients, good results were obtained in each after a second operation was performed to remove the tube. Lahey and Pyrtek,[9] of the Lahey Clinic, described the technics of splitting the head of the pancreas to locate the lower end of the divided duct so that an end-to-end reconstruction can be carried out. In 19 of 27 patients (73 per cent) operated upon by this technic, results were good or excellent. Fifty-nine (78 per cent) of 78 patients undergoing simple end-to-end repair obtained good results. The authors also reported that a plastic (Heineke-Mikulicz) procedure to open short stenosed segments of the duct gave uniformly successful results in 17 patients, and that duct-to-intestine anastomoses performed in 45 patients gave worthwhile results in 33 patients.

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Aust and Varco[4] point out the advantages of bringing the long arm of the T tube out through a separate incision in the wall of the duct and allowing a short limb to extend through the intact anastomosis. Of their 11 patients, results were good in eight when the drainage was managed in this fashion, while the results were good in only 40 per cent of these patients when the T tube was brought out through the anastomosis.

Procedures and Results

Between 1940 and 1955, 89 operations* for injured bile ducts were performed at the Cleveland Clinic Hospital, of which 69 (performed on 58 patients) could be classed as *reparative*. These 58 patients also had undergone 108 operations elsewhere, totaling 197, or an average of 3.4 operations per patient. Four (4.5 per cent) patients died in the postoperative period.

Of the 69 reconstructive procedures, 21 were hepaticoduodenostomies; 19 were simple dilatations with insertion of a T tube; 12 were end-to-end anastomoses; seven were hepaticojejunostomies; five were Roux-Y procedures; and five employed either a Vitallium tube prosthesis, skin grafting, or the Grindlay procedure (Table 1). The best results were obtained in the first group,

Table 1.—*Comparison of results of 69 reparative operations on the common bile duct*

Operation	Total number of operations	Good Results**	
		Number of operations	Percentage, %
Hepaticoduodenostomy	21	18	86
Dilatations	19	11	58
End-to-end anastomosis	12	7	58
Hepaticojejunostomy	7	3	43
Roux-Y procedures	5	3	60
Vitallium tube prosthesis	2	0	—
Skin-graft reconstruction	2	0	—
Grindlay procedure	1	0	—
Total	69	42	60

***Patient doing well, having no chills, fever, or jaundice.*

where 18 patients are classified as having obtained "good results"—feeling well, with no chills, fever, or jaundice. Two of the three patients in whom operative results were not good had intermittent symptoms of cholangitis without jaun-

**Eighty-seven of these operations were performed by three surgeons: George Crile, Jr., M.D., Stanley O. Hoerr, M.D., and Thomas E. Jones, M.D. (now deceased).*

dice, and subsequently underwent gastric resections (Billroth II) to exclude the biliary tract from the direct alimentary flow. The other patient had recurrent jaundice and required reoperation; this result is classed as a failure. The other procedures—dilatation, end-to-end anastomosis of the duct, hepaticojejunostomy, and the use of internal skin grafts (2 cases), Vitallium tubes (2 cases), or the Grindlay procedure (1 case), each produced satisfactory results in less than 60 per cent of the cases.

Technic

Irrespective of the sites of previous incisions, a right subcostal approach gives the most direct access to the common bile duct. If the previous incision was made through the rectus muscle, the subcostal incision lies lateral to the previous one, and the abdomen can be entered almost extraperitoneally without disturbing intraperitoneal adhesions. After the liver is identified, the adherent structures are dissected from its undersurface from right to left (Fig. 1). When carried out

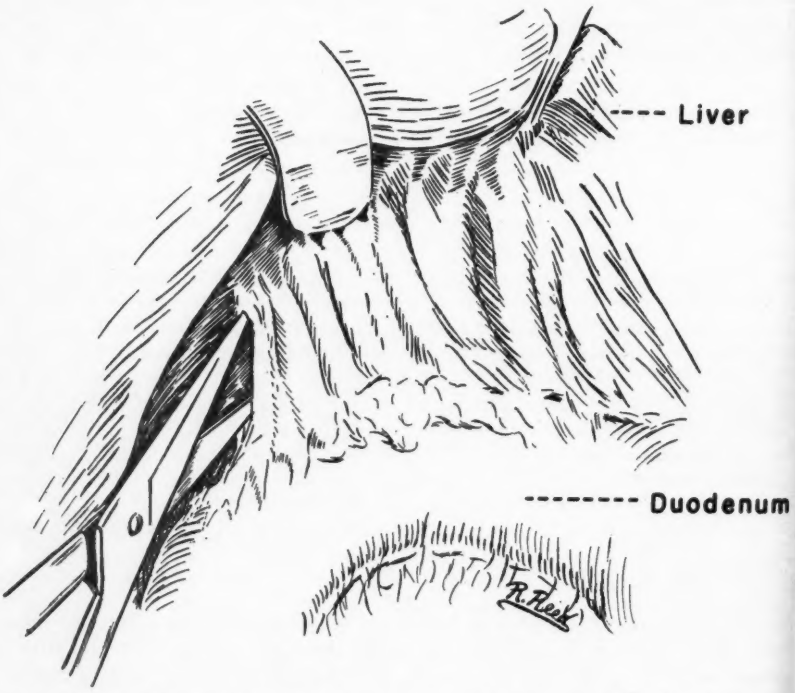

Fig. 1. Sketch showing the beginning of lateral dissection of subhepatic adhesions, for hepaticoduodenostomy.

in this fashion, the dissection proceeds rapidly, and loss of blood is minimal. As the porta hepatis is approached, the hepatic artery can be identified by palpation (Fig. 2). When this vital landmark is identified, aspiration with a needle

Fig. 2. Sketch showing how the pulsation of the hepatic artery is palpated as dissection progresses during hepaticoduodenostomy.

inserted lateral to it usually demonstrates the bile-containing duct, and an operative cholangiogram can be made (Fig. 3). The information obtained from the cholangiogram may facilitate further dissection of the duct.

Unless the ends of the duct are unusually accessible and of good caliber, hepaticoduodenostomy is carried out using a single layer of interrupted 00 chromic catgut sutures on atraumatic needles to effect an end-duct-to-side duodenal anastomosis (Fig. 4). Silk should not be used in repair of the duct because this material may serve as a nidus for stones that can produce biliary obstruction that requires reoperation (Fig. 5). Although we prefer to insert the T tube through the wall of the duct and place it with a limb extending through the anastomosis, occasionally the stump of the proximal duct is short and it is necessary to bring the tube out through the anastomotic line. Under these circumstances the T tube should not be pulled out, rather, it should be cut off at the level of the skin and should be allowed to pass through the intestinal tract.

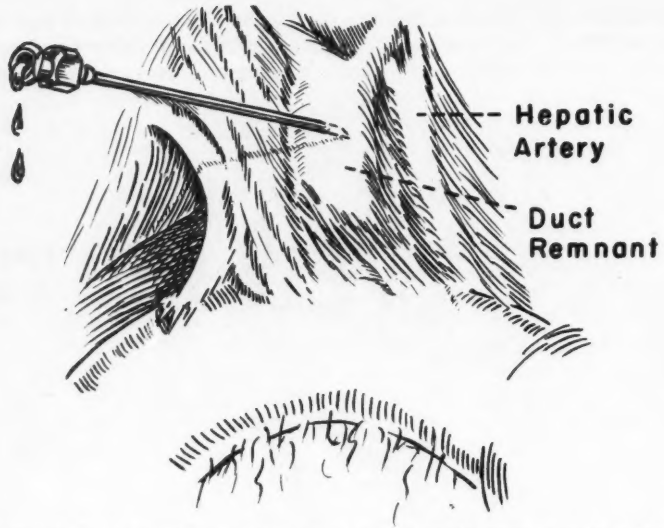

Fig. 3. Sketch showing needle aspiration lateral to the hepatic artery in order to locate the duct containing bile, for hepaticoduodenostomy.

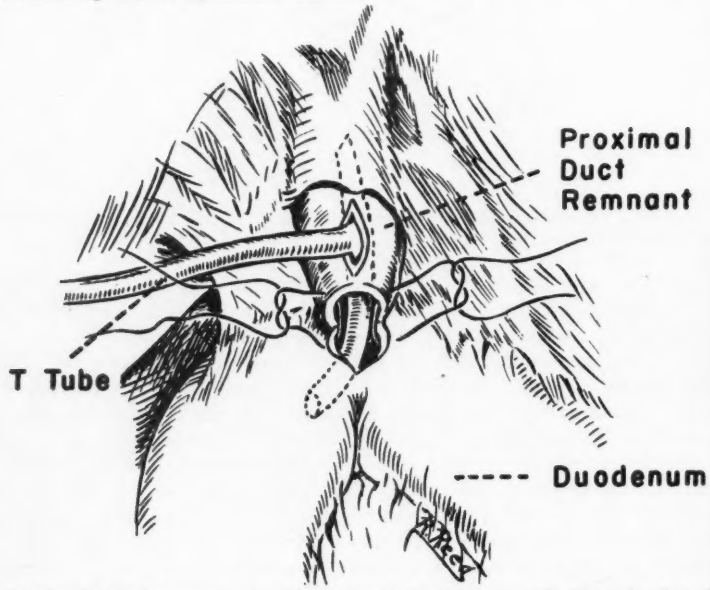

Fig. 4. Sketch showing completion of the hepaticoduodenostomy. The posterior line of interrupted chromic catgut sutures has been placed, and the anterior line has been started.

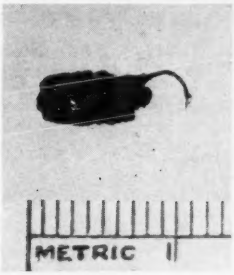

Fig. 5. Gallstones formed around silk suture used in repairing the common bile duct.

This maneuver may result in less disruption and, hence, less stricturing of the anastomosis. We have had no experience with the internal drainage tubes of Allen and McArthur.

If the stump of the proximal duct is fairly large (1.5 cm. or more in diameter), a hepaticoduodenostomy can be done without a T tube, but the area should be drained. Should the injury to the common duct occur at the time of cholecystectomy, when the tissues are soft and pliable, it is best simply to reconstruct the duct over a T tube placed into the duct above or below the line of anastomosis.

Conclusion and Summary

Since selection of cases and use of various special technics for the repair of common bile ducts are apt to influence the end results of operations on the common bile duct, it is impossible to state categorically which is the best method of repair in all cases. In our reported series of 69 operations however, hepaticoduodenostomy was most often feasible and gave results that were better than those of other methods.

The simplest approach to the damaged duct is through a subcostal incision, dissecting the undersurface of the liver from right to left. Fine chromic catgut is the suture material of choice. The most acceptable type of internal splint is the standard T tube which, whenever possible, should be brought out through a separate opening and not through the anastomotic line.

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EXFOLIATIVE CYTOLOGY AS AN AID TO THE DIAGNOSIS OF GASTRIC CARCINOMA

A Preliminary Analysis of 116 Cases

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GASTRIC carcinoma is increasingly important because of the diagnostic and the therapeutic problems it raises and the high annual mortality—40,000 persons[1]—in this country. Because of this high mortality many surgeons advocate drastic surgical therapy for all potentially malignant lesions in the stomach. Ochsner and Blalock[2] believed that all gastric ulcers should receive surgical treatment, and warned of the great responsibility assumed by the physician who institutes conservative treatment of an ulcerative gastric lesion. Ravdin[3] and others are of a like opinion.

The reported five-year survival rate for all patients having carcinoma of the stomach has varied from 1 to 15 per cent.[4,5] The Cleveland Clinic rate for the years 1940 through 1945 was 7.1 per cent. With the more frequent and, at times, extensive resections being performed for the past 10 years, a greater number of patients are selected for operation and the five-year survival rate should be higher.[6-8] For a personal series of 53 patients with gastric carcinoma who underwent gastric resections for cure, Hoerr,[9] at the Cleveland Clinic, has had a five-year survival rate of 36 per cent.

The low survival values have been thought to result, in part at least, from the difficulty of obtaining an early diagnosis. Certainly, the detection of the disease at a stage when more favorable resections can be performed is dependent upon its recognition before metastasis or marked local extension occurs. Routine screening by roentgen examination of the stomach, as done on 7,500 patients at Johns Hopkins Hospital and on 7,500 control subjects in North Carolina[10] (screening program sponsored by the American Cancer Society), proved the procedure to be impractical. Obviously there is great need of a method for earlier diagnosis of gastric carcinoma.

In addition, there is need of a more accurate method of diagnosis of gastric carcinoma. The accuracy of roentgen diagnosis in most centers is from 60 to 70 per cent, while that of gastroscopy usually is less. The accuracy of combined roentgen and gastroscopic examinations is higher—approximately 80 per cent.

Our interest in improving diagnostic accuracy led us to use exfoliative gastric cytology as a diagnostic approach. Raskind,[11] Rubin, Klayman, and

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Kirsner,[12] and Klayman and associates[13] reported greater than 90 per cent accuracy of exfoliative cytology in the diagnoses of more than 1,700 patients. At The University of Chicago Clinics the surgeons have such confidence in the findings on gastric cytology that in several patients they have resected the stomach on the basis of the cytologic report alone, even though all other preoperative findings and the stomach itself grossly at operation appeared normal. In those few patients, pathologic examination of the resected specimen revealed a barely discernible lesion.

Gastric cytology was used half a century ago, but it did not become clinically dependable until recently. This procedure has evolved from simple aspiration of gastric contents with smears being made for cytologic evaluation; to mechanical abrasion of the gastric walls with ingeniously devised balloons and brushes;[14-18] to gastric lavage with mucolytic agents such as papain[16] and chymotrypsin;[13,19] to a simple gastric lavage technic using an acetate buffer solution.

Initial attempts at cytologic evaluation by simple smears of gastric contents failed because of the overabundance of debris, and autolysis of cells by the enzymatic content of gastric juice. The various abrasive technics have not been satisfactory, in our opinion, because of the difficulty in placing the abrasive balloon and also the uncertainty that the appropriate areas were reached by the instrument; antral lesions particularly are difficult to diagnose by these technics. Three years ago Rossmiller[20] undertook the use of the Ayre brush technic in approximately fifty cases. Results were so consistently incorrect that the procedure was abandoned.

Technic

Our exfoliative cytologic technic involves no special equipment, and the financial cost to the patient is moderate. The equipment consists of a plastic disposable Levin tube, an Asepto aspirating syringe, a 100-ml. plunger type of syringe, a few lengths of rubber hose, a sink aspirator (mechanism of the type commonly employed in a laboratory), a bucket, and a supply of ice.

The patient is prepared by fasting from midnight before the test, except that he is encouraged to drink water. He is intubated orally with a standard disposable plastic Levin tube. Contrary to the recommendations of some,[21] we do not use an Ewald tube, or prepare the patient with barbiturates, narcotics, or topical anesthetics. When the Levin tube is properly placed, it is secured with adhesive tape and the stomach is aspirated. This fasting aspirate is not used for smears,[21] but is discarded. The stomach is then washed with from 500 to 1,000 ml. of tepid tap water in 100-ml. amounts and each of these aspirates is discarded. This lavage rids the stomach of much debris and permits making much "cleaner" slides. The lavage is discontinued when the aspirated solution becomes practically crystal clear, and 500 ml. of acetate buffer solution is immediately introduced into the stomach. The Levin tube is then clamped and the patient is rotated 360 degrees during a 10-minute period. After this rotation, the Levin tube is connected to a sink aspirator through a bypass 500-ml. flask

that has been packed in ice and has been chilling since the start of the procedure to slow down cellular digestion. The solution is then removed in its greatest amount, usually from 200 to 300 ml. which, with the sink aspirator, requires approximately five minutes. This collection constitutes the "total buffer" solution which is centrifuged. Slides are prepared of the pooled sediment.

After the collection of the "total buffer" solution, the Levin tube is connected to a 100-ml. syringe. The "last drop" of solution is recovered after repeated flushing of the stomach with the residual fluid. This collection usually amounts to from 20 to 30 ml. of specimen, the richest in cellular content. After this last collection the Levin tube is withdrawn and discarded. The specimen is transmitted to the Cytology Laboratory in a bucket of ice.

The securing of the specimen requires from 15 to 20 minutes. We have noted no cellular degeneration as a result of the few minutes' delay involved in transporting the specimen to the laboratory; we believe that this is most important because it eliminates the need for centrifuging the specimen and preparing the slides at the site of collection. A technician does not collect the specimen; we believe that only the physician who is familiar with gastric carcinoma can give the attention so necessary for obtaining a satisfactory specimen. When the collection of the cellular specimen is made by a physician, as in the study reported here, and is delivered as an unknown to the cytopathologist, there can be no subjective influence on the interpretation of the cellular forms.

After we had used the procedure in a few cases, we found that more satisfactory material could be obtained with the use of the simple acetate buffer solution than with the acetate buffer with chymotrypsin[19] added as a mucolytic agent. Our cellular collections have been better with the acetate buffer solution than with the plain saline solution. We have noted, as have others, that the acetate buffer solution develops a sediment after standing for some time. Others[21] have filtered the solution. We found this sediment to be a mold that can be avoided by proper refrigeration that preserves the acetate buffer solution for an indefinite period without sediment.

Results

During the nine-month period from September, 1957, to June, 1958, 116 consecutive patients underwent exfoliative cytology. Although this group is not sufficiently large nor is the follow-up (of patients not operated upon in whom the cytologic findings were negative) sufficiently long to be of statistical value, the results are indicative.

In 79 of the 116 patients, the cytologic findings were negative and no operation was performed. In none of these patients were there any clinical (including roentgen) indications of malignancy. Many of the examinations were performed as controls to improve our cytologic technic and methods. Twenty-four of the 79 patients had gastric ulcers that were thought to be benign clinically, were associated with ample gastric acidity, and appeared benign on roentgenography; progress roentgen examinations in these patients have shown the gastric ulcers to have healed completely. Progress cytologic studies can give

added reassurance to the clinician treating a gastric ulcer that appears entirely benign clinically, gastroscopically, and roentgenographically. Cytologic studies were done in some patients who had received cobalt-60 teletherapy for complicated peptic ulcer,[22] but in whom there was no evidence of neoplasm.

Thirty-seven of the 116 patients have been operated upon. It must be noted that the cytologic studies of these patients include first efforts with this technic. Most patients were chosen for cytologic examination because they had some type of gastric abnormality that on the basis of other findings might require surgical treatment.

In Table 1 the rates of accuracy of the findings by exfoliative cytology and roentgenography in the 37 patients who underwent operation are compared,

Table 1.—*Comparison of accuracy of findings by exfoliative cytology and by roentgenography in 37 patients*

Pathologic diagnosis, number of patients		Cytologic diagnosis		Roentgen diagnosis		
		Inaccurate, number of patients	Accurate, number of patients	Inaccurate, number of patients	Accurate, number of patients	Indeterminate, number of patients
Benign lesions	23	2	21 (91%)	7	14 (64%)	2
Malignant lesions	14	1	13 (92.9%)	0	12 (86%)	2
Total	37	3	34 (92%)	7	26 (70%)	4

and in Table 2 the gastroscopic findings are summarized. The one falsely negative cytologic report was on a patient with widespread carcinoma of the stomach with extension into the distal esophagus. The Levin tube could not be

Table 2.—*Gastroscopic findings in nine patients with carcinoma*

Findings	Number of patients
Accurate	7
Unsatisfactory examination (considered erroneous diagnosis)	1
Inaccurate (benign lesion reported as carcinoma)	1

well placed because of some esophageal obstruction, and the collection of material was not rigidly controlled. This falsely negative report is considered to have resulted from poor collection technic rather than from improper cytologic evaluation. Gastric cells were not present on the slides. Because of

this experience our cytologists now indicate whether or not gastric cells are present for evaluation.

In the series there was a total of 15 patients on whom reports were rendered. There were two falsely positive cytologic reports on washings for patients with clinically active gastric ulcers that had been considered benign by conventional evaluation. Both of these patients were operated upon and specimens from each showed dysplastic changes; one patient had received cobalt-60 teletherapy (Case 4).

Illustrative Cases

Case 1. A 66-year-old man was examined in November, 1957, because of epigastric distress of two weeks' duration. The pain had its onset after meals and was relieved by food or alkali. He had had arteriosclerotic heart disease, old posterior myocardial infarction, and angina pectoris. Roentgen examination of the stomach showed an ulcer crater in the fundus with some rigidity of the wall of the distal portion with a lack of peristalsis in the antrum, indicating the possibility of neoplasm (Fig. 1). A hemogram was normal. On gastric analysis after alcohol stimulation, there was 18 units of free hydrochloric acid. Exfoliative gastric cytology showed no tumor cells.

Fig. 1. (Case 1.) Roentgenogram shows ulcer crater in the fundus and some narrowing and irregularity of the antrum. Although cytologic findings were normal, operation was advised because of the appearance of the antrum and the ulcer. Histologic study showed no evidence of cancer.

On November 21, 1957, a transgastric biopsy of the gastric ulcer and a posterior gastroenterostomy were performed. The pathologic report of the biopsy specimen was chronic gastritis with superficial glandular dysplasia. The patient had an uneventful postoperative course and was discharged eight days postoperatively. On January 2, 1958, six weeks after operation, the patient suddenly died, presumably as a result of myocardial infarction.

Comment. The cytologic examination of this patient was among the first that we performed, and we did not yet have confidence in its diagnostic accuracy. The operation was of little value to the patient since he did not have carcinoma; he died six weeks later with a myocardial infarction. If more reliance had been placed on the cytologic diagnosis, operation would have been avoided.

Case 2. A 73-year-old man was first examined here in February, 1958, because of episodes of fullness and gas beneath the sternum one hour after breakfast, which were relieved promptly by belching, and anterior chest pain precipitated by exertion and relieved by nitroglycerin. There was no history of gallbladder colic. The diagnoses were generalized arteriosclerosis with arteriosclerotic hypertension, arteriosclerotic heart disease with angina pectoris, gallstones, small sliding hiatal hernia, and questionable intramural neoplasm of the gastric fundus.

Roentgen examination revealed a small sliding hiatal hernia. The distance between the top of the gastric fundus and the left leaf of the diaphragm was increased, and there was some loss of the normally rounded contour of the fundus. It was considered that these changes represented an intramural type of neoplasm (Fig. 2). The hemogram was normal, and on gastric analysis free acid was present in the fasting specimen. Exfoliative gastric cytology was reported as showing no tumor cells.

Fig. 2. (Case 2.) Roentgenogram suggests a tumor in the cardia. The distance between the diaphragm and the cardia was increased, also suggesting the presence of neoplasm. Cytologic findings were normal. At operation, patient had an enlarged spleen with adhesions between the spleen and diaphragm producing the deformity seen on the roentgenograms.

At operation on April 1, 1958, the spleen was found to be enlarged two to three times its normal size. The spleen was adherent to the diaphragm next to the hiatus, and this adherence produced the filling defect in the fundus of the stomach consistently seen on roentgen examination. The stomach itself was normal.

Cholecystectomy was performed. The patient had an uneventful postoperative course and was discharged on the eighth postoperative day. When he was last examined in May, 1958, one month after operation, he was asymptomatic.

Comment. Since this 73-year-old patient had no history of gallbladder colic or other

serious symptoms referable to the gallstones, the chief surgical indication was the suspected carcinoma of the stomach. As in Case 1, if we had had more confidence in the diagnostic accuracy of cytologic examination, operation might have been avoided.

Case 3. A 74-year-old man underwent a "routine check-up" in October, 1957. He had a gastric resection for gastric ulcer in 1925, following which he had no digestive symptoms. Roentgen examination showed that the stomach had been approximately half resected and then anastomosed to the jejunum (Fig. 3). There were prominence and irregularity of the mucosal folds and the stomach had a stiff appearance, most likely as the result of infiltrating neoplasm. Gastroscopic examination revealed fixation of the walls of the stomach as evidenced by lack of insufflation. Also, high in the stomach on the anterior wall, a moundlike formation of tissue with a white exudate was observed, suggestive of neoplastic tissue. According to the gastroscopist there was probably diffuse gastric neoplasm without involvement of the esophageal cardiac junction.

Fig. 3. (Case 3.) Roentgenogram shows evidence of stiffening and loss of the normal mucosal pattern in a patient who had gastric resection for ulcer 33 years previously. Gastroscopic findings suggested diffuse neoplasm and cytologic findings were abnormal. At operation, an extensive nonresectable gastric carcinoma was found.

The laboratory findings showed an anemia: an erythrocyte count of 2,830,000 per cu. mm., a cell volume of 32 ml. per 100 ml., and a hemoglobin content of 10.0 gm. per 100 ml. Findings on exfoliative gastric cytology were positive for atypical cells compatible with malignancy.

On October 25, 1957, a transabdominal biopsy was performed and the posterior and lesser curvatures of the stomach were seen to be involved by an ulcerating infiltrating lesion adherent to the left lobe of the liver and to the posterior parietes. A large lymph node lying in the gastrohepatic ligament alongside the hepatic artery was involved by tumor. A biopsy of the gastric tumor was reported as showing undifferentiated carcinoma.

Comment. Exfoliative gastric cytology was diagnostic in this patient, but in view of the findings on roentgen and gastroscopic examinations, surgical treatment would have been advised without the cytologic findings that supported the roentgen and gastroscopic diagnoses.

Case 4. A 61-year-old man was examined in March, 1958, because of ulcer-like distress that had occurred for a few weeks each spring for the past four years. The distress consisted of epigastric burning two hours after meals, and was relieved by antacids and food. The hemogram was normal and, on gastric analysis, after administration of Histalog, there was 36 units of free hydrochloric acid.

Roentgen examination revealed an ulcer, high on the lesser curvature of the stomach, which was considered to be benign (Fig. 4). Gastroscopic examination revealed an ulcer crater just proximal to the angle. The crater was 1½ cm. in diameter and had a sharp well-defined edge surrounded by a zone of erythema. The base of the ulcer was covered with a white membrane. A few folds of mucosa were seen radiating into the upper perimetry. The ulcer was considered to be benign by gastroscopic examination.

Fig. 4. (Case 4.) Roentgenogram shows gastric ulcer that appears benign. Cytologic findings were positive for dysplastic cells. At operation the ulcer appeared benign, but severe dysplasia was seen in the fundus, pyloric antrum, and vestibule. The patient received one treatment with cobalt-60 before the first cytologic study, and five treatments before the operation, all of which were directed at the gastric fundus to decrease acid secretion.

As a supplement to intensive medical treatment[23] this patient was given cobalt-60* teletherapy,[22] starting on March 21, 1958. After the first cobalt-60 treatment, gastric cytology revealed cells compatible with malignancy. Three days later and after four cobalt-60 treatments, cytology was repeated and cells that were considered to be dysplastic were observed. Because of the cytologic findings, operation was advised. A two-thirds gastric resection (Billroth I) and a biopsy of the gastric fundus were performed on March 31, 1958. During operation, a direct smear of the ulcer was taken and spreads were made and stained by the Papanicolaou method; they showed dysplastic cells.

The pathologic examination of the biopsy specimen from the fundal mucosa revealed no evidence of neoplasm or dysplasia, but there were many parietal cells. The pathologic examination of the resected portion of the stomach, which contained the ulcer crater,

**The radioactive cobalt used was supplied by Oak Ridge National Laboratory on authorization of the Isotopes Division, United States Atomic Energy Commission, Oak Ridge, Tennessee.*

revealed chronic peptic ulcer of the anterior lesser curvature of the fundus of the stomach; severe dysplasia of the gastric mucous membrane of the fundus, pyloric antrum, and vestibule; and chronic inflammation of the lymph nodes. Postoperatively, the patient had a superficial wound infection that healed fairly promptly and he was discharged on the sixteenth postoperative day.

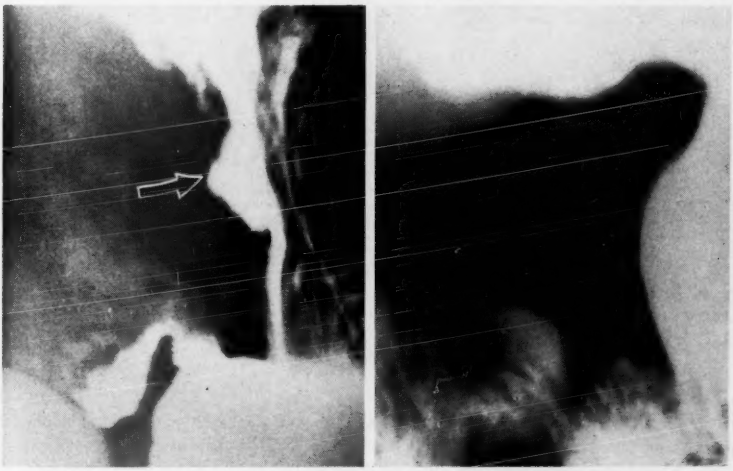
The patient was examined in May, 1958, two months after operation, at which time he was completely asymptomatic and was advised to return to work.

Comment. This patient had dysplasia after only one treatment, and again after four treatments with cobalt-60 teletherapy. Cytologic studies in nine patients during and after cobalt-60 teletherapy have shown dysplasia in one case, nuclear changes in one, and have been normal in seven cases after cobalt-60 teletherapy used to reduce the acidity in benign ulcer. The relation between dysplasia in the stomach and the subsequent development is not clear.[24] Until we know that gastric dysplasia is not a precursor of gastric carcinoma, patients with this type of cytologic change must be treated as though they have potentially malignant lesions. Further studies on the effect of cobalt-60 teletherapy on gastric cytology are being conducted here.

Case 5. A 47-year-old woman was first examined in January, 1958, in the Department of Orthopedic Surgery because of pain in the upper lumbar area. She had epigastric distress radiating into the back intermittently for 12 years. This distress was unrelated to meals and had been more severe during the previous two years.

Laboratory findings were normal except for a hypochlorhydria on gastric analysis (free hydrochloric acid −18 units after stimulation with histamine). Exfoliative gastric cytology showed no neoplastic cells. Roentgen examination showed a large gastric ulcer on the lesser curvature, at the posterior wall near the cardiac end of the stomach.

The location of the gastric ulcer would have required an extremely high resection, and the roentgen and cytologic examinations both suggested a benign ulcer (Fig. 5A).



A B

Fig. 5. (Case 5.) **A.** Roentgenogram indicates a moderately sized ulcer crater high along the lesser curvature near the cardia. There was no filling defect and the ulcer appeared benign. Cytologic findings were negative. **B.** Roentgenogram six weeks later indicates complete healing of the ulcer crater. Cytologic findings again were negative.

Intensive medical therapy[23] supplemented by cobalt-60 teletherapy[22] was instituted and within three days the patient was asymptomatic.

Examination six weeks later showed that the patient had remained entirely asymptomatic; cytologic findings were negative for neoplastic cells, and roentgenography showed complete healing of the ulcer (Fig. 5B). On gastric analysis after the injection of histamine, there was achlorhydria, indicating the effect of the cobalt-60 teletherapy.[22] In June, five months after starting treatment, progress studies (roentgenography of stomach and cytology) were again normal.

Comment. Negative findings on cytologic examinations, associated with roentgen and clinical evidence of a benign ulcer, supported the clinician in advising and continuing conservative medical treatment. The proper decision concerning treatment (medical or surgical) was extremely important to the patient, since she would have required a high resection for a benign lesion.

Some of the cytologic and histologic features encountered are demonstrated in Figures 6 through 9.

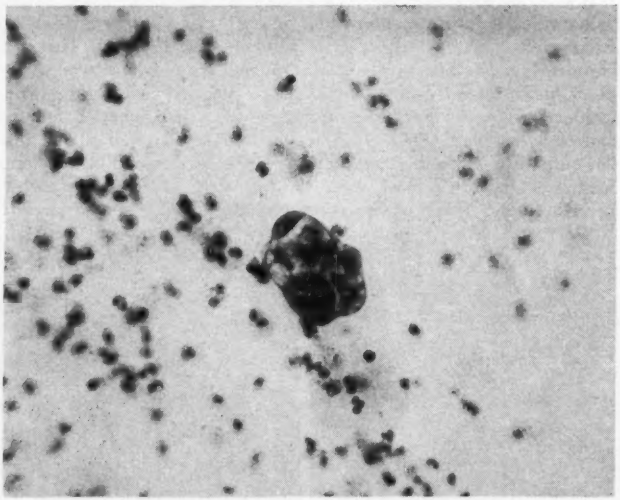


Fig. 6. Neoplastic mucus-containing cells from signet-ring cell carcinoma of the stomach. Papanicolaou stain; x 425.

Indications for Gastric Cytology

Much has been written regarding the role of gastric cytology in the field of cancer detection. On the basis of our experience, we believe that this procedure should not be routine but should be used in the following situations:

(1) For diagnosis when there is a possibility on the basis of clinical (including roentgen) findings of neoplastic change in the stomach.

(2) For the annual or even semiannual screening of patients with premalignant lesions such as pernicious anemia, polyposis (when effective operative procedures cannot be done), and achlorhydria.

(3) For follow-up evaluation of cellular changes following irradiation for nonneoplastic conditions.

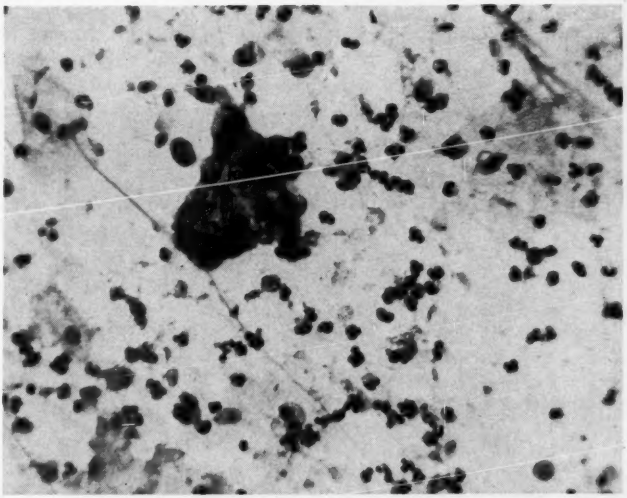


Fig. 7. Cluster of darkly stained cells from undifferentiated carcinoma of the stomach. Papanicolaou stain; x 425.

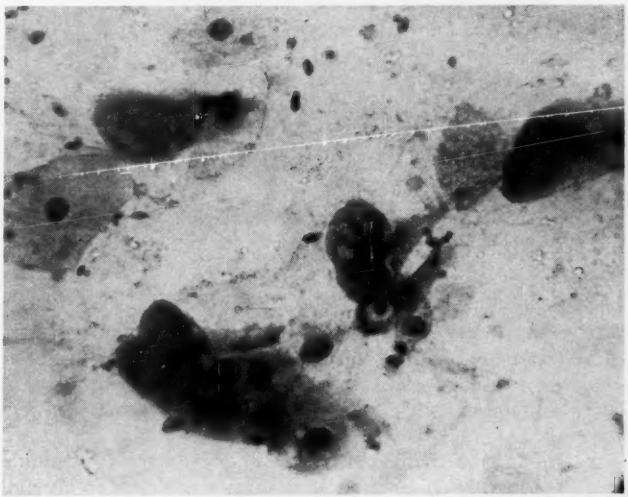


Fig. 8. (Case 4.) Atypical cells that may be erroneously interpreted as neoplastic. Papanicolaou stain; x 425.

(4) For a possible research tool in the further evaluation of cellular changes as one of the fundamental processes in the development of carcinoma.

(5) For confirmation of the gastric origin of a neoplasm evident as a metastatic carcinoma.

(6) For supportive evidence for trial on medical treatment of patients with clinically and roentgenographically benign gastric ulcers.

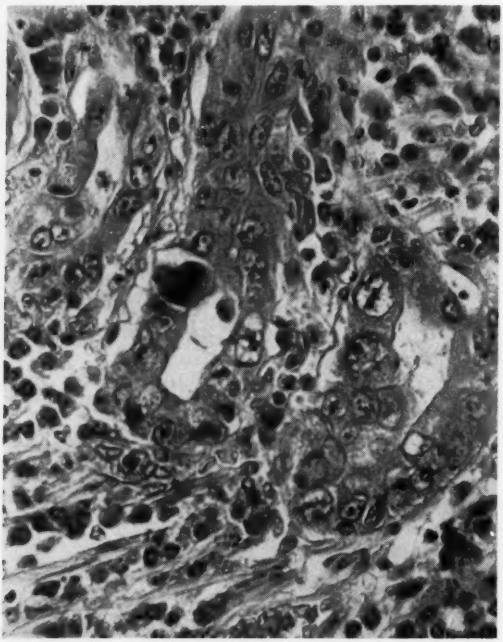


Fig. 9. (Case 4.) Histologic specimen of gastric lesion that was the source of cells in Figure 8. Carcinoma in situ or irradiation reaction? Pathologically, the latter diagnosis was favored. Hematoxylin-eosin and methylene blue stains; x 425.

Summary

Exfoliative gastric cytology was performed on 116 patients, using a revised method of collection and an acetate buffer solution. To obtain good results with gastric cytology, two conditions are essential: (1) securing an adequate specimen, and (2) obtaining competent cytologic interpretation. Each is worthless without the other.

In 79 of 116 patients, there was no clinical or roentgen indication of gastric neoplasm and the cytologic findings were negative. However, the findings on cytologic examinations in this group can be considered only "presumptively correct" because none of the 79 patients underwent operation.

Thirty-seven of the 116 patients underwent operation, and on the basis of the findings on pathologic examination are considered "proved cases." The accuracy of the preoperative cytologic diagnoses in these 37 patients was 92 per cent; there were two false positive and one false negative reports. This high rate of accuracy indicates the practical importance of exfoliative gastric cytology in the diagnosis of carcinoma of the stomach.

The indications for employing exfoliative gastric cytology correspond with any suspicion of the presence of a gastric neoplasm. More widespread use of the technic should result in more accurate and earlier diagnoses of gastric carcinoma.

Acknowledgment

The authors are indebted to Walter L. Palmer, M.D., Joseph B. Kirsner, M.D., Howard Raskind, M.D., and co-workers at The University of Chicago, for stimulating interest and giving liberally of their time and knowledge in setting up the aspiration technics.

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CHRONIC URTICARIA AND DENTAL INFECTION

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CHRONIC urticaria often is a most puzzling process of obscure origin, since it may arise from many different causes. It is customary to consider the role of infection, emotions, and also allergy to common substances in the environment, particularly drugs. The relation of active dental infection to chronic urticaria frequently is sought, yet there are few detailed reports of the incidence and importance of such a relationship.[1] We therefore undertook to study chronic urticaria in a group of patients who had been given complete dental examinations, to see how often dental infection occurred, and the effect of eradication of dental infection when present.

Method of Study

Records of 100 patients with chronic urticaria who had been referred to our dental department were reviewed to determine the incidence of dental infection present, and whether or not there was a correlation between appropriate dental treatment and the course of the urticaria.

Criteria. For the purpose of this study, chronic urticaria is defined as persistent or recurring urticaria, with or without angioedema, of more than four weeks' duration. The eruption had been present for many weeks or months in most cases; up to 10 years in several cases, and intermittently from childhood in a few adults. The cause was obscure in all cases. Some patients had been referred to the dental department in the search for foci of infection, and some patients had been referred because of dental symptoms and signs noted at the time of the initial complete examination.

Alveolar abscess is defined as roentgen evidence of bone resorption at the root end of a tooth. Advanced periodontal disease is defined as the loss of the supporting bone structure of the tooth to more than two thirds of the length of the root, or involvement of the bifurcation of multirooted teeth as determined roentgenographically. The extent of dental caries also was noted.

Since most of the patients were referred to the Cleveland Clinic for study, the recommended dental treatment was not carried out here. A few patients who did receive dental surgery were followed, and the course of the urticaria was recorded.

Analysis of Records

Age and sex of patients. The ages of the 100 patients ranged from 10 years to 79 years. Table 1 lists the distribution by decades. There were 62 males and 38 females.

Table 1.—*Ages of 100 patients with chronic urticaria and dental infection*

Age range, years	Number of patients
10-19	3
20-29	13
30-29	27
40-49	31
50-59	24
60-69	1
70-79	1
Total	100

Dental disease. Chronic alveolar abscesses were present in 35 patients, in 22 males and in 13 females. Advanced periodontal disease was present in 28 patients, in 21 males and in seven females. Both alveolar abscesses and periodontal disease were present in 13 patients. Fifty patients had no evidence of dental infection. Caries was extensive in 34, moderate in 19, and slight in 22 patients.

Seventeen patients with chronic dental infection were treated and were adequately followed. The course of the chronic urticaria was unaffected in 11. It disappeared after dental surgery in six patients and remained absent for follow-up periods of from one month to 13 years. Urticaria recurred subsequently in three of the six patients after 13 years, 11 months, and 3 months respectively.

Comment

Chronic dental infection in 50 of 100 patients with chronic urticaria is a high incidence, which may be related to the selection of cases. The treated patients reviewed in this series are too few to indicate the coincidental or causative relation of dental infection to urticaria. Certainly the lack of effect on the urticaria from removal of the infection by extraction in the 11 patients indicates the absence of an etiologic correlation in this group, if indeed the infection was completely eradicated.

Since the course of chronic urticaria is notoriously unpredictable, it is difficult to evaluate the part played by dental infection in producing urticaria in the six relieved patients. For example, a 40 year-old woman who had hives intermittently for six years, and who was found to have chronic alveolar abscesses, retained roots, and rampant caries, had no treatment whatsoever, and the urticaria disappeared after the initial studies were completed.

The courses of three treated patients illustrate the problems of interpretation.

Examples

Case 1. A 47-year-old man had asthma persistently since the age of 32 years. He had urticaria and angioedema for 10 months prior to examination here, with remission for no

more than three days at a time. Physical findings were within normal limits except for carious teeth. Allergy studies yielded no clue to a possible drug, food, or inhalant mechanism for the hives. Dental studies showed a periapical abscess associated with a badly carious upper left cuspid. After extraction of this tooth, urticaria disappeared promptly and remained absent during the six-year follow-up period. Asthma cleared completely for one year and then returned in a mild degree.

Comment. Such a case gives rise to the idea of an etiologic role of dental infection in urticaria and also, at times, in asthma, although the mechanism is obscure.

Case 2. A 35-year-old man had recurrent "giant hives" for more than two and one-half years when first examined in 1937. The longest interval of freedom from urticaria was two and one-half months. Physical and laboratory findings showed no abnormalities. Dental findings showed a horizontally impacted lower third molar with some evidence of bone rarefaction around the coronal portion. Later, acute local infection developed and the molar had to be removed. The urticaria ceased abruptly. He had no urticaria for 13 years. In 1949 however, he again had hives. Potential dental infection was discovered associated with an extensively carious lower left second molar. Despite appropriate treatment, urticaria continued to the time of the last follow-up in 1957.

Comment. The prompt and persistent clearing of urticaria after dental surgery suggests an important relationship to dental infection at that time. The appearance of hives 13 years later, without change after dental treatment, suggests a different cause for urticaria, and possibly suggests a coincidental correlation with the initial dental infection. The case also illustrates the need for prolonged follow-up for a complete evaluation.

Case 3. A 36-year-old man, who had asthma since childhood and also ragweed hay fever and allergic vasomotor rhinitis, had persistent urticaria and angioedema for nine months prior to examination in 1954. No dental infection was discovered, but an unerupted, impacted, lower right third molar had to be removed. Urticaria cleared promptly and had not returned nine months later.

Comment. In this patient, urticaria ceased after dental surgery for an anatomic abnormality without evidence of dental infection. The importance of nonspecific operative stress is suggested as a consideration in the cases of infection followed by relief of symptoms.

Urticaria may be considered to be a pattern of reaction to many different stimuli, as suggested by unpredictable remissions and exacerbations. Perhaps once the pattern has become established, a susceptibility to recurrence always remains, similar to the pattern of recurrence of asthma as indicated by Rackemann's[2] studies. Even though the importance of dental infection in urticaria is not clear, search for such infection seems indicated in patients with stubborn urticaria of obscure origin, since prompt clearing occasionally does follow indicated dental surgery. Moreover, such treatment improves the patient's general health.

A review of the incidence of dental caries showed 53 patients with moderate-to-marked or rampant susceptibility to caries.

Summary and Conclusions

Evidence of chronic dental infection was found in 50 of 100 patients with chronic urticaria. After dental treatment of 17 patients, urticaria was unchanged

in 11, was relieved in six with subsequent return of urticaria in three, in 13 years, 11 months, and three months, respectively.

The course of the treated patients in this small series does not suggest a frequent or important relationship of dental infection to urticaria, although occasionally gratifying relief of symptoms may follow appropriate dental treatment. The dental treatment should be complete with removal of the demonstrated infection, repair of other salvable teeth, and replacement of the missing teeth so that optimal function of mastication and oral health may prevail.

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MAGNETIC TAPE-RECORDING ELECTROPHYSIOLOGIC MONITOR

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THE clinical use of an instrument that records the electrocardiogram continuously for long intervals[1] indicated the desirability of constructing a multichannel monitoring device that displays several physiologic phenomena simultaneously and records them on magnetic tape. The design and construction of a recording and monitoring device for the study of physiologic functions involved the following engineering problems: (1) picking up and amplifying information that is available only at low levels; (2) recording and reproducing low frequencies and slowly varying functions; (3) blanking and electronic switching to permit observation of several functions simultaneously; (4) displaying functions on the screen of a large cathode ray tube; (5) circuitry that creates a minimum of artifacts and rejects externally induced artifacts (such as power-line interference and contact potentials); (6) maximum ease of operation and dependability of the instrument.

This report describes and discusses the multichannel monitoring devices that we have developed and have used for three years.

Figure 1 is a block diagram and Figure 2 is a photograph of the first instrument that was developed. The magnetic tape recorder has four recording heads, four reproducing heads and one erase head. The tape speed is 1⅞ inches per second, permitting more than eight hours of continuous recording. The tape-transport mechanism is mounted as a drawer.

Low-Level Amplification

The electrocardiographic amplifiers were specially designed to operate with minimal voltages and currents on the elements, thus permitting low operating temperatures and consequent minimal deterioration of tubes and other components. Stability is obtained by means of regulated power supplies to plate and heater. The amplifiers are direct-coupled, have a maximum voltage gain of about 10,000 and are brought into direct-current balance by means of resistance potentiometers. Balance is indicated by a zero-center meter. When properly balanced, the amplifier is highly insensitive to potentials that do not appear between its input terminals.

Low-Frequency Recording

Recording of low frequencies on magnetic tape is accomplished by using a carrier current of a frequency that can be conveniently recorded and repro-

This study was supported in part by grants from the Cleveland Area Heart Society.

duced in an ordinary manner. The carrier is amplitude modulated by the information that is to be recorded. The modulated carrier is picked up from the tape by the reproducing head and is amplified and demodulated to yield the originally recorded information.

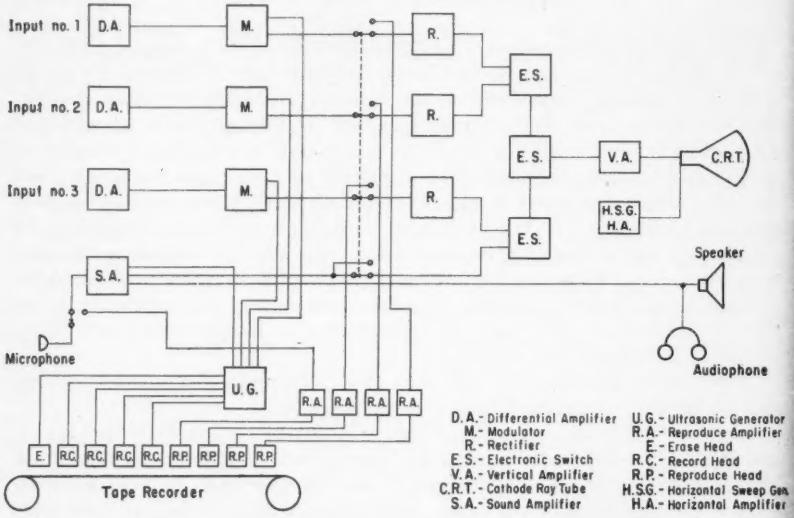

Fig. 1. Block diagram of magnetic tape-recording electrophysiologic monitor.

The modulating and demodulating systems are unusual in that the carrier current is a square wave of 600 cycles. The modulator is a partially balanced device that is free of distortion even at 100 per cent modulation. The modulator units are similar to the electronic switches used in the deflection system, except that the electronic switches operate at 1,000 and 2,000 cycles instead of the 600 cycles of the modulators. The square-wave carrier has the advantage of simplicity of generation and control, and ease of removal of the carrier from the information by means of a full-wave demodulator and a simple resistance-capacitance filter. In this method of demodulation, the carrier is largely removed by cancellation, and the extent of carrier cancellation depends only on the rise time of the square wave and the balance of the demodulator. The tops of the carrier waves contain all modulations in full detail, even though they have a much higher frequency than that of the carrier. When the negative half of the cycle is reversed by the full-wave demodulator, this negative half of the carrier cycle falls precisely into place between two adjacent positive halves, thus returning all information to its original form with the addition of a sharp switching pulse occurring at double the frequency of the carrier. This pulse is of such short duration that a small amount of filtering easily removes it.

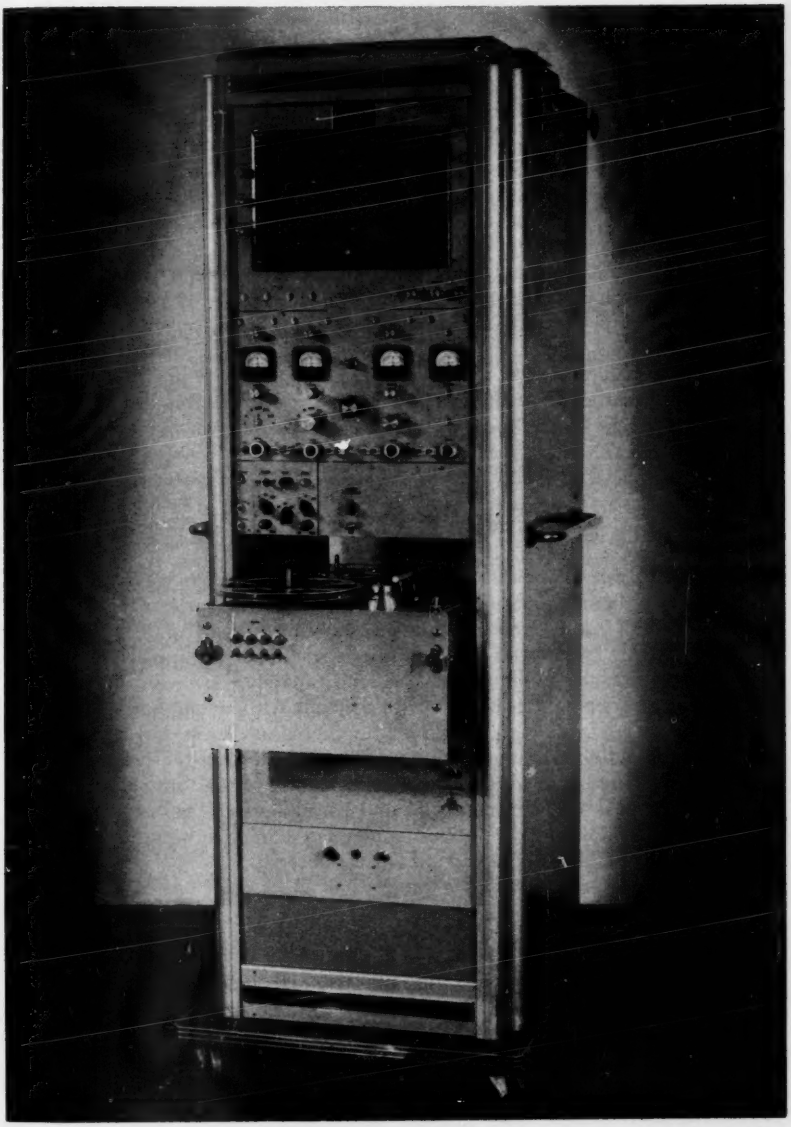

Fig. 2. Photograph of monitor.

The modulated carrier, as reproduced from the magnetic tapes, does not have the fast rise time of the original modulated square wave. However, the third and the fifth harmonics are retained approximately in their original magnitudes and phases. The system is capable of recording and reproducing information accurately at frequencies as high as half the frequency of the carrier, because of the phase and magnitude equalizations used in the reproduce amplifiers. A tape speed of 1⅞ inches per second is employed but, with faster tape speeds, higher orders of harmonics of the carrier are retained, and still higher frequencies of information can be reproduced from the tape, even at the same carrier frequency.

Amplitude modulation of the carrier, compared to frequency modulation or some other form of modulation in time, has the advantage of being insensitive to variations in tape speed. This characteristic is important, because it is difficult to maintain the constant tape speed at the slow rate of 1⅞ inches per second, selected to permit the long, unattended recording time required. Amplitude modulation has the disadvantage of being sensitive to irregularities in the surface of the tape. Therefore, the tape must have uniform magnetic coating and a smooth finish for satisfactory reproduction.

Stability Considerations

It was advisable to use as much direct coupling as possible to assure minimal ringing. When direct coupling is used throughout, there is an optimal situation for realization of instant recovery from any extreme voltage excursions brought about by switching, lead changes, and other operational manipulations, and all responses to control are instantaneous. Unfortunately, however, it seems impossible to make dependable contact with the body without generating a contact potential. Any contact potential can readily be balanced out, but usually such a potential is not constant, and causes a slow variation in the position of the base line. Therefore, one coupling condenser is incorporated into each channel to restore the base line automatically and continuously. The use of only one condenser, or a minimum of coupling condensers, minimizes ringing, and much of the simplicity of direct-coupled circuits is retained.

Large Screen Cathode Ray Tube

In monitoring it is advantageous to use large-screen cathode ray tubes when multiple functions are to be displayed. The electronic switching of the beam of a single electron gun permits the use of magnetic deflection, which in turn makes it possible to use a standard television picture tube that has been provided with the necessary long-persistence phosphor. The horizontal sweep speed is variable over a range of 1/100 second to 10 seconds. The high sweep speeds are used to resolve the high frequencies and fast rise times of the electronic switches for test purposes, and the slower sweep speeds are used for displaying physiologic functions.

Blanking and Electronic Switching

The difficulty of magnetically deflecting the electron beam at extremely high speeds makes it desirable to blank the electron beam during the electronic switching interval. This is accomplished by differentiating the output of the vertical amplifier, and using the resulting pulses to cut off the electron beam during the switching intervals. As a result of this blanking, the traces are sharper and clearer.

To produce the four independent traces on the screen of the cathode ray tube, the outputs of two identical electronic switches are connected to the two inputs of a third electronic switch unit that is identical with the first two except that it operates at a frequency approximately twice that of the other two switches. Under these conditions, four traces are formed on the cathode ray screen, each trace being made up of short dashes occurring at approximately one-millisecond intervals. Each of these traces responds only to the signal applied to one of the four corresponding inputs of the first two electronic switches; they may be positioned as desired by means of three positioning controls on the panel.

Operation

The instrument is operated almost as though it were four independent instruments. Only necessary controls are brought out to the front panel, and each control has evident effects that are easy to understand. The screen traces are controllable as to brightness, focus, sweep rate, and position of trace. The amplifiers have gain and balance controls; the balance, as mentioned previously, is indicated by a zero-center meter.

Portable Model

A smaller instrument was built to fill a need for a device that would take up less space and would be more readily portable. It is essentially a copy of the original instrument (Fig. 3). Its principal differences lie in the use of a much smaller two-channel tape-recording mechanism and a 5-inch electrostatically deflected cathode ray tube. The complete unit weighs about forty pounds. One channel is arranged to record and reproduce low-frequency functions such as the electrocardiogram, and the other is utilized for frequencies in the audible range up to about 2,500 cycles. This latter channel is used primarily for recording cardiac sounds and speech. During the recording process, the information being recorded on both channels may be simultaneously monitored on the screen of the cathode ray tube, and the sound channel may be monitored by stethophone as well. The front panel controls on the portable unit are similar to those on the large four-channel instrument. Amplifier balance, however, is indicated by the simultaneous ignition of two small neon lamps.

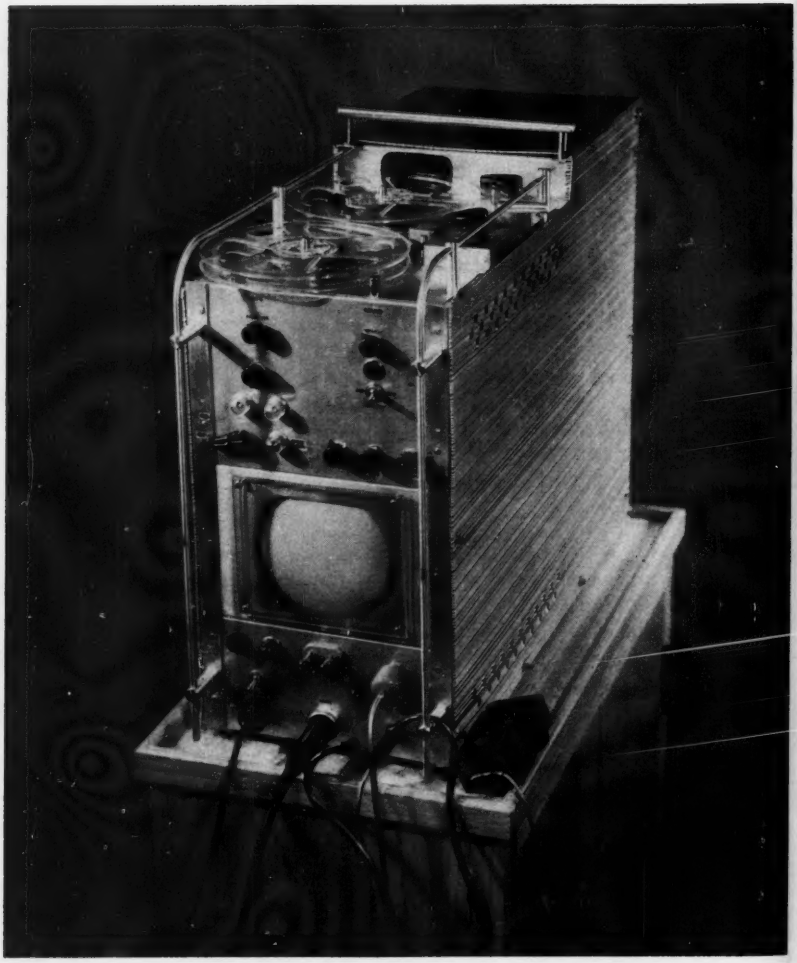

Fig. 3. Photograph of portable monitor.

Applications

With the aid of special transducers and the addition of relatively simple circuitry, it has been possible to display a variety of information on the large screen of the cathode ray tube and at the same time to record the information. Among these phenomena are the electrocardiogram, the vectorcardiogram, the

stethogram of cardiac sounds, the electroencephalogram, the ballistocardiogram, the myogram, and arterial pressure curves. Traces may be recorded by photographing the face of the cathode ray tube or by feeding the information into a suitable string or D'Arsonval galvanometer. The recorded information can be reproduced any number of times and observed in the same manner as it was while it was being recorded. The ability to visualize the stethogram and electrocardiogram reproduced simultaneously, facilitates the teaching of auscultation of the heart, because it enables the student to secure proper timing simply. Small loops of magnetic tape may be used for studying cardiac sounds.

Summary

Multichannel magnetic tape-recording instruments have been developed for monitoring physiologic functions. Problems encountered in the development of this type of equipment are outlined and solutions are presented. Electrocardiograms, vectorcardiograms, electroencephalograms, stethograms, ballistocardiograms, arterial-pulse curves and electromyograms have been recorded.

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PHARYNGOESOPHAGEAL DIVERTICULUM

A Comparison of Results Obtained by Inversion and by Excision

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THE objective of treatment of esophageal diverticulum is to relieve the dysphagia and regurgitation with the least risk of mediastinitis, infection of the wound, recurrence of the diverticulum, or injury to laryngeal and sympathetic nerves. Since excision, inversion, or elevation of the diverticulum all relieve the major symptoms, the selection of the type of operation depends upon its safety and prevention of recurrence. We have studied records of a small series of patients treated either by excision or by inversion to determine which of these two methods is the safer and more reliable.

Pathogenesis and Symptoms

Pharyngoesophageal diverticulum is a pouchlike herniation of the pharyngeal mucosa and submucosa through a weak region in the musculature of the distal hypopharynx. This rare condition occurs predominantly in men during the fifth to the seventh decades of life. Its pathogenesis was well understood and described by Stetten[1] and by Jackson and Shallow[2] in the early part of this century. The predisposing factors are: (1) a structural weakness of the tissues that are located between the oblique fibers of the posterior portion of the inferior constrictor muscle and the transverse fibers of the cricopharyngeus (Fig. 1); (2) a degenerative relaxation of the elastic tissue of the hypopharyngeal wall; this relaxation is said to be aggravated by pressure against the cervical vertebrae;[3] and (3) an in-co-ordination of the function of the cricopharyngeus.[4]

The cricopharyngeus is a sphincteric muscle, which Jackson and Shallow[2] called a "pinchcock," for it occludes the upper esophagus during respiration. During normal swallowing, as the powerful peristaltic wave progresses distally through the constrictor muscles, the cricopharyngeus relaxes in response to a reflex arc that originates in the upper posterior pharyngeal wall, and is transmitted via the pharyngeal plexus, nucleus ambiguous, spinal accessory nerve, ganglion nodosum, and vagus nerve. However, when there is in-co-ordination in the relaxation of the cricopharyngeus in response to this reflex, an increased pharyngeal intraluminal pressure may produce a protrusion of mucosa and submucosa through the weakness just proximal to the obstructing cricopharyngeus.

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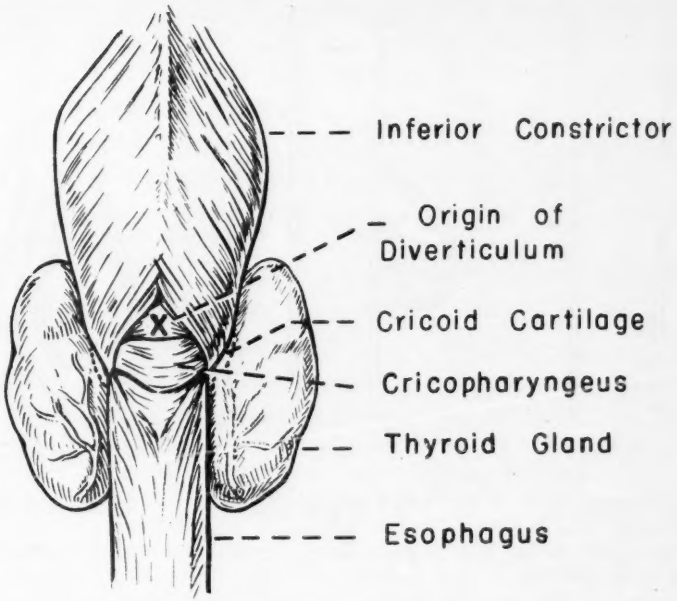

Fig. 1. Diagram illustrating the posterior pharynx and the most common site of origin of a pharyngoesophageal diverticulum.

By the pulsion of repeated swallowing, a small simple sac develops, producing a sensation of obstruction, as by a foreign body, or fullness in the throat which requires clearing of the throat. Large particles of food may "hang up" in the throat. These symptoms are transient and intermittent. The roentgenogram shows a simple midposterior sac at the level of the sixth cervical vertebra, with the orifice of the sac perpendicular to the axis of the esophageal lumen. No regurgitation or dysphagia is present. Lahey and Warren[5] define this early stage in the formation of the diverticulum as stage I (Fig. 2).

The herniation slowly progresses to stage II; the sac lengthens and its fundus is forced downward into the left side of the neck between the prevertebral and pretracheal fascia. When the pouch becomes dependent it retains swallowed food, and new symptoms result.

As the volume of the sac increases it is accompanied by a sensation of greater fullness in the neck. Dysphagia is absent, but gurgling noises from fluid in the sac often embarrass the patient. Furthermore, when the patient is recumbent the retained food flows into the pharynx and the mouth, where it may be regurgitated, swallowed, or aspirated. Nocturnal regurgitation and aspiration may result in such complications as bronchitis, pneumonia, bronchiectasis, pulmonary abscess, or chronic laryngitis. A roentgenogram after a barium

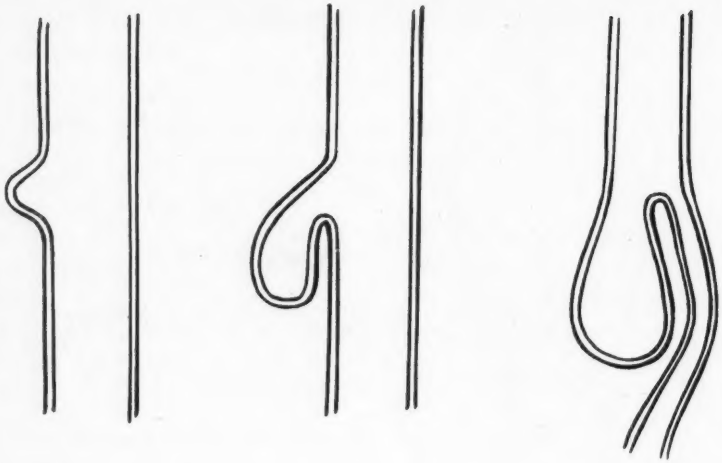

Fig. 2. Stages in the development of a pharyngoesophageal diverticulum (diagrams after Lahey and Warren[5]).

swallow demonstrates a transverse slitlike orifice in the pouch which is perpendicular to the esophageal orifice, and a dependent sac that retains barium.

Usually, after several years, the weight of the material retained in the sac drags its fundus toward the mediastinum. The orifice of the diverticulum now lies in the axis of the pharyngeal lumen, while the esophageal lumen is distorted and becomes perpendicular to the pharyngeal lumen. At fluoroscopy, barium is seen to descend in the pharynx into the diverticulum to fill it, and then to spill over into the proximal esophagus. In this stage III (Fig. 2), swallowing is obstructed, and the chief symptoms are dysphagia and regurgitation of most solid food. Although liquids are tolerated for a time, loss of weight and inanition may ensue. Eventually, complete esophageal obstruction may result. If the pouch enters the mediastinum, symptoms of fullness in the chest, dyspnea, palpitation, suffocation, coughing, and choking may occur. Rarely carcinoma or diverticulitis may occur in the pouch.

Treatment

Evolution of treatment of pharyngoesophageal diverticulum:

1877 *Diverticular-cutaneous fistula* established by Nicoladoni[6] of Vienna.

1885 *One-stage excision* first successfully performed by Wheeler.[7]

1895 *Inversion* first employed by Girard.[8]

1907 *Two-stage excision* to prevent mediastinitis introduced by Goldmann.[9]

1910 (Stetten[1] summarized reports of the first 60 treated cases: 16 per cent operative mortality and only 40 per cent primary healing of wounds.)

1917 *Diverticulopexy* performed by Hill.[10]

1921 *Inversion* used by Bevan.[11]

1934 (McClure[12] reported laryngeal obstruction from an inverted sac.)

1933-1953 *Two-stage excision* popularized by Lahey,[5] who proved its safety and reliability in 365 cases.

1945 *One-stage excision* proved to be safe and reliable by Harrington,[13] and in

1947 by Sweet,[14] and by King.[3]

1944 *Inversion* revived by Ross,[15] and in

1951 by Crile and Robnett.[16]

Treatment of patients in our series. From 1946 through 1957, two of us (G. C., Jr., and L. K. G.) operated on 37 patients who had pharyngoesophageal diverticula, employing a one-stage excision or an inversion procedure. Eighteen patients were treated with inversion procedures as described by Crile and Robnett.[16] A purse-string suture is placed around the neck of the sac, and just before the sac is inverted an Ewald tube is passed into the esophagus to outline its junction with the sac. Flexing the patient's neck facilitates passage of the tube. The tube is then partially withdrawn and the pouch is inverted into the pharynx. The base of the sac is closed by drawing tight the purse-string suture and the tube is passed again to insure against stricture. The muscularis of the pharynx is closed over the inverted sac with interrupted sutures, and the wound is closed, usually without drainage.

Nineteen patients were treated with one-stage excisions. The technic is a modification of that described by Sweet.[14] An Ewald tube is introduced into the esophagus before the neck of the sac is clamped. The neck of the sac is then progressively excised proximal to a Kocher clamp and is closed with interrupted silk sutures. A second layer of sutures repairs the muscularis. The wound always is drained with a soft-rubber drain for three days. Penicillin and streptomycin frequently are administered until the patient is discharged on the fifth postoperative day.

Results

The 37 patients who were surgically treated have been followed for periods from several months to nine years. Of 18 patients treated with inversion procedures, 12 report excellent results with complete relief of symptoms and no complications (Table 1). Only one patient had a serious complication—a wound infection followed by recurrence of the sac and dysphagia for dry foods. One patient had a small abscess in the wound; one patient reports slight difficulty in swallowing pills and dry food. Two patients, who had large 90-cc. diverticula (5 by 10 cm.), occasionally sense the presence of the inverted sac which they

described as a "tab moving up and down in the throat when belching." Roentgenograms show that one patient had a small (1-cm.) pocket at the site of inversion, but this caused no symptoms.

Table 1. — *Results of treatment for pharyngoesophageal diverticulum by inversion or by excision in 37 patients*

Results*	Surgical procedures, no. of cases	
	Inversion	Excision
Excellent, asymptomatic	12	14
Slight dysphagia	1	2
Intermittent sensation of presence of inverted sac	2	0
Wound abscess	1	1
Wound abscess, recurrence, moderate dysphagia	1	0
Recurrence, symptomatic	0	1
Recurrence (1 cm.), asymptomatic	1	0
Horner's syndrome	0	1
Recurrent nerve paralysis	0	0
Total	18	19

**No deaths occurred in this series.*

Of the 19 patients treated with one-stage excisions, 14 report excellent results; they had uncomplicated postoperative courses and are asymptomatic. One patient had an abscess in the wound. In one patient a recurrence required reoperation. Two patients have difficulty in swallowing pills and dry foods. One patient had a transient Horner's syndrome that affected the right side.

Comment

In all of the patients in this series a one-stage operation was employed. The chief argument for using a two-stage procedure is to avoid mediastinitis. However, the treatment for mediastinitis due to a leak of the cervical esophagus is cervical incision and drainage; thus, if a one-stage excisional repair is drained adequately, this complication is avoided by prophylaxis.

Ross,[15] and Crile and Robnett[6] described how large inverted sacs will contract, atrophy, and cause little trouble; however, in our small series two patients who had large sacs are conscious of the inverted sacs occasionally when they belch. Therefore, excision is preferable in patients with extremely large sacs. On the other hand, when an extremely small diverticulum is found, the sac often constitutes only a small mucosal "bump," and from a practical point of view, it seems meddlesome to do more than invert such a sac. Sacs of average size can be treated satisfactorily either way.

Summary

It appears that two-stage operations for pharyngoesophageal diverticula are no longer required. Either inversion or excision of the sac is equally safe and satisfactory for most diverticula. However, large sacs are best treated by excision, and small sacs are best treated by inversion.

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PULMONARY BLASTOMYCOSIS: A REPORT OF A CASE TREATED WITH 2-HYDROXYSTILBAMIDINE

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NORTH American blastomycosis may exist as a cutaneous or a systemic disease. In the systemic form the organs most frequently affected are the lungs and the bones; however, other organs are affected in a significant number of cases.[1] The disease may have many and bizarre manifestations and has even been reported as having simulated multiple myeloma, with an increase of plasma cells in the bone marrow.[2] The epidemiology is poorly understood and no definite conclusions as to the reservoir or mode of transmission have been established. It is believed that the causal organism, a fungus, resides in moist soil and that humans contract the systemic type of blastomycosis by inhalation, and the cutaneous type by primary inoculation of exposed surfaces.[3-5]

It was previously thought that the cutaneous form was more prevalent, but in a recent series of 40 patients only four had isolated skin lesions.[2] The most frequent symptoms were cough, hemoptysis, expectoration, and fever. Our report is of a case of pulmonary blastomycosis in which the primary symptom was fever, and which was complicated by chest pain and hemoptysis secondary to a pulmonary embolus.

Report of a Case

History. A 46-year-old man, an office worker from southwestern Ohio, was admitted to the Cleveland Clinic Hospital on January 21, 1957, with a chief complaint of fever of about one month's duration. In November, 1956, he had a fever of short duration associated with a sore throat, which responded to penicillin. He again had a sore throat and fever in mid-December, and was hospitalized; he stated that he had "virus pneumonia." While in the hospital he had a daily temperature of 101 to 102°F. He stated that he had had no cough, hemoptysis, or chest pain. During the hospitalization a diagnosis of diabetes was made and he was given insulin.

For three years he had "arthritis," which started with pain in the jaws, and in the last year had consisted of pain and stiffness in the hands and wrists. For the past year he had taken prednisone four times daily, and previous to that he received corticotropin (ACTH), cortisone, and gold salts. The administration of prednisone had been discontinued at the time he was hospitalized for pneumonia, and his joint symptoms then became worse.

Chief Medical Resident.

Physical findings. The temperature was 101.8°F.; the pulse rate was 100; and the blood pressure was 130/70 mm. of Hg. The patient had a Cushingoid facies and phlebitis near a recent cut-down site on the left ankle. Examination of the lungs disclosed a few moist rales and decreased breath sounds at the base of the right lung. The joints were tender and a sensation of heat was present over the wrists, elbows, and left shoulder. There was minimal swelling of soft tissue over the left knee and ankle. There was moderate limitation of motion of the above-mentioned joints, and he had a weak grasp.

Clinical findings. The hemoglobin was 13.5 gm. per 100 ml.; leukocyte count was 13,300 per cu. mm. with 66 segmented cells, 7 stab cells, 21 lymphocytes, and 6 monocytes. Urinalysis showed a pH of 7.5, a trace of albumin, no sugar, occasional erythrocytes, and from 4 to 6 pus cells. The erythrocyte sedimentation rate (Rourke-Ernstene method*) was 2.05 mm. per min.; blood urea nitrogen was 21 mg. per 100 ml.; a fasting blood sugar was 135 mg. per 100 ml.; transaminase was 21 units; serum protein was 6.6 gm. per 100 ml., with 3.45 gm. of albumin and 3.15 gm. of globulin; serum polysaccharides were 236 mg. per 100 ml. Results of a blood test for lupus erythematosus were negative. Two blood cultures were sterile. Sputum smears and cultures were negative for acid-fast bacilli and fungi. Results of histoplasmin and blastomycin skin tests were negative, and an intermediate strength PPD** was positive. Results of complement fixation tests for blastomycosis, histoplasmosis, and coccidioidomycosis were negative. Biopsy specimens of skin and muscle tissue showed no evidence of pathologic changes. A chest roentgenogram showed an infiltration in the right lower lobe (Fig. 1).

Hospital course. The patient's diabetes was well controlled with 15 units of NPH† insulin daily. He was started on a program of ACTH, chloroquine phosphate, and prednisone for the arthritis. His daily afternoon temperature was from 101 to 102° F. throughout his stay in the hospital.

Two days after admission the patient experienced a sudden onset of left pleuritic pain; the following day he coughed up bloody sputum. Examination of the lungs showed decreased breath sounds and rales at both bases, and a left pleural rub; the patient was splinting the left side of the chest. Another roentgenogram of the chest at this time showed evidence of a pulmonary infarction in the left lower lobe of the lung. The area of infiltration in the right lower lobe was thought to be indicative of a neoplasm; bronchoscopic findings and bronchial washings were essentially normal. The right middle lobe could not be visualized by bronchography.

A right thoracotomy was performed on February 11, 1957, and the process was found to be inflammatory. The biopsy specimen showed caseous necrosis, and organisms suggestive of *Histoplasma capsulatum* or *Blastomyces dermatitidis* were

*Normal is 0.65 mm. or less per minute.

**Purified protein derivative.

†Neutral protamine Hagedorn.

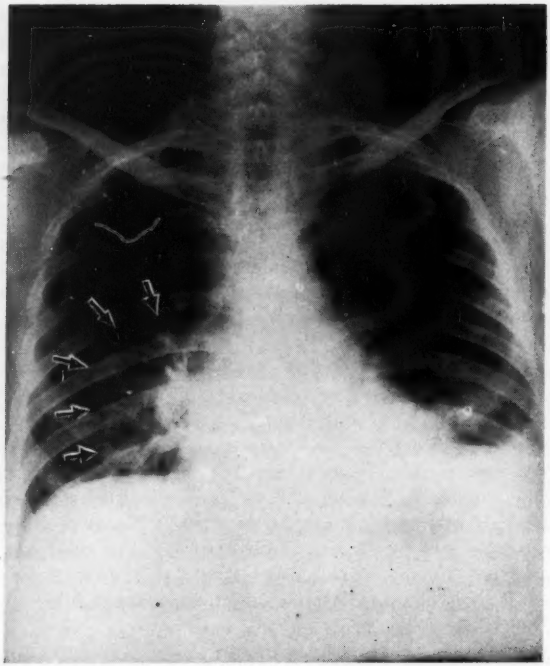

Fig. 1. Photograph of the first roentgenogram showing the discrete, faintly outlined lesion in the right lower lung field.

demonstrated by the Gridley stain (Fig. 2). Cultures of the specimen from the pulmonary biopsy produced *B. dermatitidis.**

The administration of steroids was stopped and the patient was given a low-purine, low-protein diet. He received potassium iodide drops orally, and was given a 10-day course of 2-hydroxystilbamidine, 225 mg. intravenously. He was discharged on February 24, 1957, still febrile and unimproved. He returned on March 8, 1957, for a second 10-day course of 2-hydroxystilbamidine, 150 mg. per day for the first five days, and 225 mg. per day for the last five days. The patient did not accept a longer course of intravenous therapy and he was discharged and advised to take potassium iodide, 60 drops per day.

On May 25, 1957, about two months after the patient had received the last dose of 2-hydroxystilbamidine, he was slightly improved with less fever. On August 1, 1957, he was afebrile; findings of an examination of the chest were normal, and a roentgenogram of the chest showed slight improvement. By December, 1957, he had gained 25 pounds, was asymptomatic, and a roent-

*Culture confirmed through the courtesy of Norman F. Conant, Ph.D., Duke University School of Medicine, Durham, North Carolina

genogram of the chest showed only residual scarring. He had a few minor pains in the hands, which were easily controlled with small doses of salicylates. At this time he returned to work.

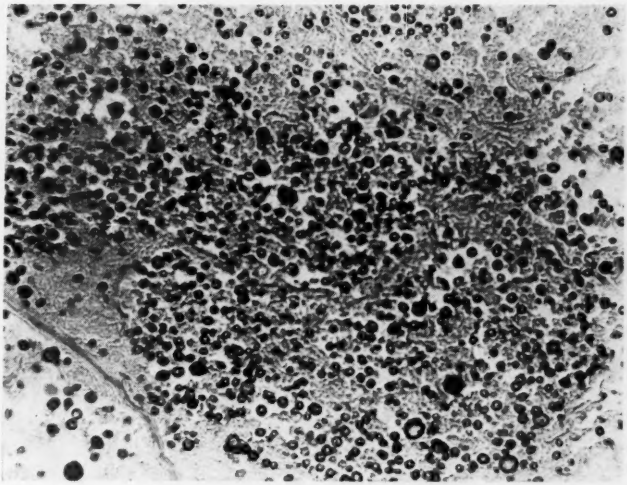

Fig. 2. Photomicrograph of the biopsy specimen of the lung showing *Blastomyces dermatitidis*. Gridley stain; x 280.

Comment

This case illustrates some of the diagnostic difficulties presented by pulmonary blastomycosis. The negative results of the skin test and the complement fixation test are not unusual findings. Martin[6] found a positive skin test in only 56 per cent of patients, and positive serologic evidence in only 53 per cent. It frequently is difficult to make a diagnosis on a tissue examination alone.[3] Our case was strongly suspected to be a bronchogenic carcinoma, which can be mimicked by blastomycosis even to the extent of rib destruction.

Prior to the use of stilbamidine, the two-year survival of patients having blastomycosis was only 8 per cent.[1] Treatment with stilbamidine or 2-hydroxystilbamidine may produce a dramatic response within a few weeks or, the full therapeutic benefit may not be noted for several months.[7,8] The delayed and prolonged response is attributed to the storage of the drug in the tissues; the drug may be found in the urine for about four months after administration has been discontinued. The recommended dosage is 150 mg. of stilbamidine, or 225 mg. of 2-hydroxystilbamidine, given intravenously. The drug usually is given daily for 30 days or in three 10-day courses with a 10-day rest between each course.[9] Toxicity to stilbamidine may be manifested by hepatic or renal necrosis, or by neuropathy most commonly affecting the trigeminal nerve. The

toxic properties of the drug are enhanced by exposure of it to sunlight, which should be avoided before and during administration. The neuropathy may also be precipitated by exposure of the patient to intense sunlight as long as three months after the last dose has been taken. Though troublesome, the neuropathy subsides within several months. The therapeutic effect of 2-hydroxystilbamidine is about one half, and its toxic effect about one sixth, that of stilbamidine, and it has not been noted to cause neuropathy.[9]

Although 2-hydroxystilbamidine has lowered the mortality in cases of blastomycosis, long-term studies have not been recorded in a sufficient number of cases for it to be properly evaluated. Harrel, Bocobo, and Curtis[8] suggest that the drug leaves much to be desired as far as a permanent cure without recurrences is concerned.

Acknowledgment

The authors express their thanks to Dr. W. T. Wilkins, Jr., of Piqua, Ohio, for his referral of this patient and for the follow-up reports.

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THREE SAFETY DEVICES FOR THE HEART-LUNG MACHINE

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THE most important single cause of pulmonary damage arising from the use of a heart-lung machine is overfilling of the pulmonary vascular bed.[1] To avoid such overfilling, the following methods and devices have been developed and are described in this paper: (1) a precise automatic control of blood volume in the oxygenator to prevent forward overloading of the lungs by changes in volume; (2) an open reservoir in the venous line to preclude the possibility of drawing the walls of the venae cavae into the openings of the cannulae, thereby occluding them; (3) a cannula in the left atrium (a) to monitor left atrial pressure, and (b) to permit release of blood from the left atrium to avert build-up of pressure and retrograde overfilling of the pulmonary vascular bed.

Automatic Control of Pump

The blood level or volume in most oxygenation chambers cannot be assessed with sufficient accuracy by the unaided eye. Since the azygos flow or "small" flow principle[2] is no longer used, large blood flows make it exceedingly trying to maintain both a smooth perfusion and a stable blood volume in the machine by manual control. At times of abrupt changes of pressure in the line, which occasionally occur, satisfactory manual control is impossible. At a flow of five liters of blood per minute, a disturbance lasting 24 seconds can increase or decrease a patient's blood volume by two liters. At the onset or at the end of a cardiac bypass, when there are no occluding tapes around the venae cavae, an abrupt overloading of the right side of the heart may take place. The increased pressure in the right side is then transmitted through the pulmonary artery to the lungs, and may lead to capillary damage within a fraction of a minute. With the high flow rate now employed, human reaction time has become too slow for adequate manual control of mechanical-heart pumps.

Present pump oxygenator. The heart-lung machine in present use here is a rotating disc oxygenator*[3] with two nonocclusive roller type of pumps,** the venous pump removing blood via an adjustable gravity-fed venous reservoir from the venous circulation, and the other (arterial pump) returning it to the arterial tree. The venous pump supplies the oxygenation chamber; the arterial pump drains it. The oxygenation chambers are 9, 13, and 20 inches long and each is 5½ inches in diameter. The pumps originally were manually controlled

Experimental work leading to this project was supported by a grant to Doctor Kolff from the Cleveland Area Heart Society.

**Björk type of oxygenator modified by Kay and Cross, manufactured by Pemco, Inc., Cleveland, Ohio.*

***Designed, made, and donated by Mr. L. C. Hercik of the Hill Acme Company, Cleveland, Ohio.*

and still can be manually regulated by two variacs* (variable autotransformers) which supply rectifiers for series field and armature current for the electric motors.**

Automatic control. A simple blood-level detector connected to the controls of the pump motors was constructed to duplicate rapidly and automatically the function of the machine operator. The detector, monitoring the blood level in the oxygenator, consists of three pointed platinum-wire electrodes and one grounded platinum-wire electrode as originally used by Clark and Gollan.[4] These electrodes make contact with the blood in a small (1-inch diameter) siliconized glass vessel connected to the oxygenator so that the level of the liquid in the glass vessel duplicates that in the oxygenator. The three platinum contacts (Fig. 1) are grouped in a $\frac{5}{8}$-inch diameter circle in a horizontal plane, and also each electrode point is vertically separated 0.5 mm. from the others. The lowest is called number 1; the center electrode, number 2; the highest, number 3. The ground or indifferent electrode projects 1 cm. below the others. All are mounted on a vertically adjustable gear rack† so that their tips can be positioned for the desired blood level in the oxygenator.

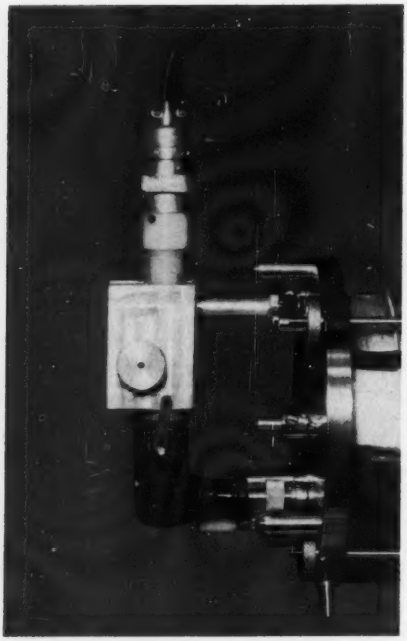

Fig. 1. Level detector. One platinum point touches the liquid in the oxygenator. The knob vertically positions all electrodes simultaneously to adjust the blood level.

**Type 1703A motor control, General Radio Corporation, Cambridge, Massachusetts.*

***D. C. Motor type DM, Master Electric Co., Dayton, Ohio.*

†Mr. Ben Matthews, Lucerne Products, Northfield, Ohio, made and donated the adjustable gear rack, and was most helpful in developing the present automatic device.

The action of the electrodes as they make or break contact with the blood surface is as follows: the lowest, number 1, turns off the arterial pump when contact is broken, and starts it when contact is renewed. The middle one, number 2, the chief regulator, increases the speed of the arterial pump when contact is made, decreases it when contact is broken. The highest, number 3, turns off the venous pump on contact, and restores action when contact is broken. The main function of the electrodes is to keep the blood level, under any condition, between the highest and the lowest electrodes, but most of the time the blood level is maintained in a slight oscillation about the center electrode. If the venous outflow tube or arterial tube is suddenly blocked during a partial perfusion, the blood volume is maintained and the perfusion rate is adjusted so quickly that there is little change in the patient's mean systemic pressure and none in the electroencephalogram.

The relation of the blood level to the electrodes is indicated by four vertically placed panel lights: flashing of the red lights at top and bottom indicates conditions needing attention; alternate flashing of the two green lights in the center (alternation signifies oscillation around the center electrode) indicates satisfactory operation. The electric circuit is shown in Figure 2. The sensing voltage is supplied by a negative 15-volt supply through 1,000,000-ohm resistors, so that from each contact no more than 15 millionths of an ampere is introduced into the blood, and the electrodes do not polarize.

Each contact operates through blood to the ground electrode bringing the grid bias of a vacuum triode to zero, thus allowing the tube to conduct. A large variation in electrode resistance such as 10,000 ohms does not affect contact action. Each tube operates a double-pole, double-throw relay; these in turn control the pumps and indicator lights.

The operator must establish a basic differential in pumping speed. Depending on the resistance of the cannula, the speed of the arterial pump may have to be twice as great as that of the venous pump. R1 is a power potentiometer whose two arms supply alternating current to the rectifiers for the series fields and armature windings of the pump motors. Its setting adjusts the difference in the speeds of the arterial and venous pumps. T1 is a single variac transformer that controls the over-all rate of perfusion. R2 establishes the two "hunting" speeds of the arterial pump. For correct operation one of these two arterial pumping rates is slightly faster and the other slightly slower than that of the venous pump. The monitor panel contains but three controls: the variac, T1, the differential potentiometer, R1, and a multiple-pole double-throw switch, S1, to shift action from manual to automatic. The panel and automatic control box are mounted between the two roller pumps (Fig. 3). Extensive testing has shown that the automatic device is reliable.

Open Venous Reservoir

There is an open venous reservoir in the tube from the venae cavae to the patient (Fig. 4). By adjustment of the height of the reservoir, the negative

pressure can be varied from 0 to 65 cm. of water (0 to 50 mm. of Hg). Occasionally rather high gravitational pull is necessary because of the use of small venous cannulae, which are preferred to large ones. When the venous reservoir is lifted above the level of the patient, it may be used for transfusion of blood.

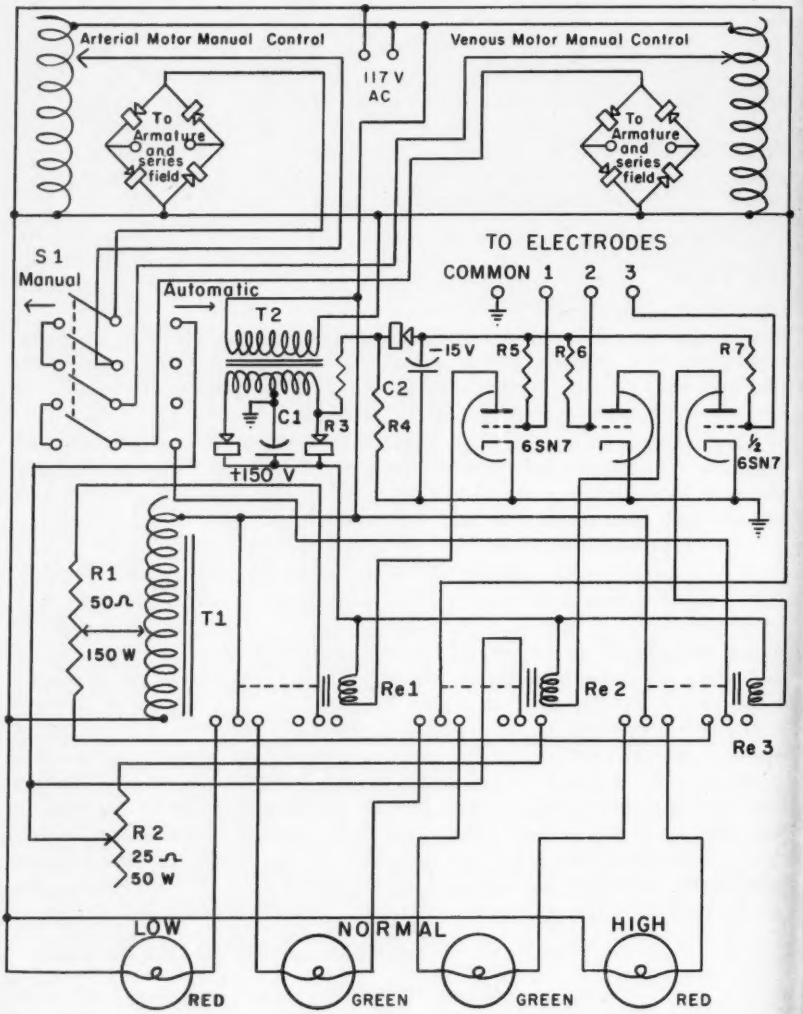

Fig. 2. Control circuit. T1, a variac transformer, controls the perfusion rate; R1 sets the difference between venous and arterial pump speeds; and S1 shifts the operation between automatic and manual.

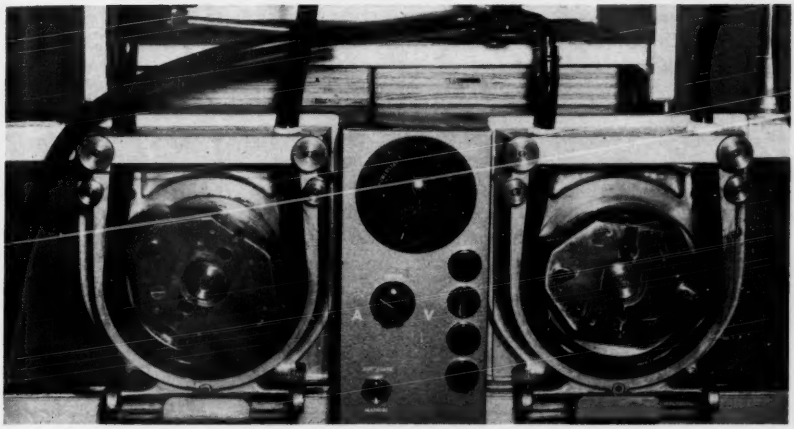

Fig. 3. Automatic control unit mounted between pumps. Location of controls is noted in Figure 4.

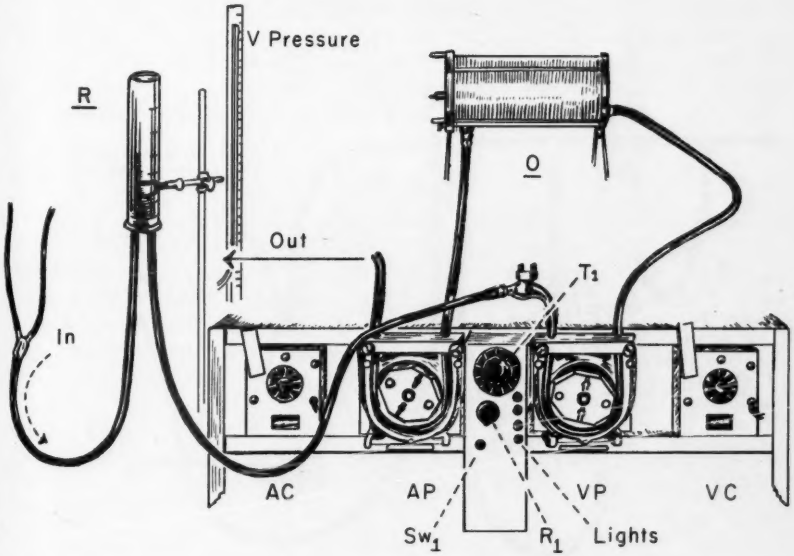

Fig. 4. Open venous reservoir, R, in the line from the patient. This is a 2-inch diameter vinyl tube, the height of which can be adjusted on the vertical rod. Near it is a manometer connected to a saphenous vein. O is the disc oxygenator, VP and AP are venous and arterial pumps, respectively, and VC and AC are their respective manual controls.

The regulation of the level in this reservoir is not automatic, but the adjustment of its height is simple. Because of its tall cylindrical shape, the blood level is easy to see; the main automatic control variac, T1, is then adjusted to maintain the level in the venous reservoir, that is, to handle all of the flow from the patient.

Left Atrial Cannula

The necessity of providing drainage from the left atrium has been recently stressed.[1] Mechanical impediment to the left atrial outflow (aortic insufficiency and mitral insufficiency) and dynamic impediment (ventricular fibrillation or ineffective left ventricular beat) may lead to retrograde pulmonary overloading with fatal capillary damage. Figure 5 shows the arrangements of the left atrial drainage.

Aspiration of the left atrial line is required only when large amounts of air have entered it. Otherwise it is sufficient to open the connecting tube to the venous reservoir; blood from the left atrium is thereby returned to the patient

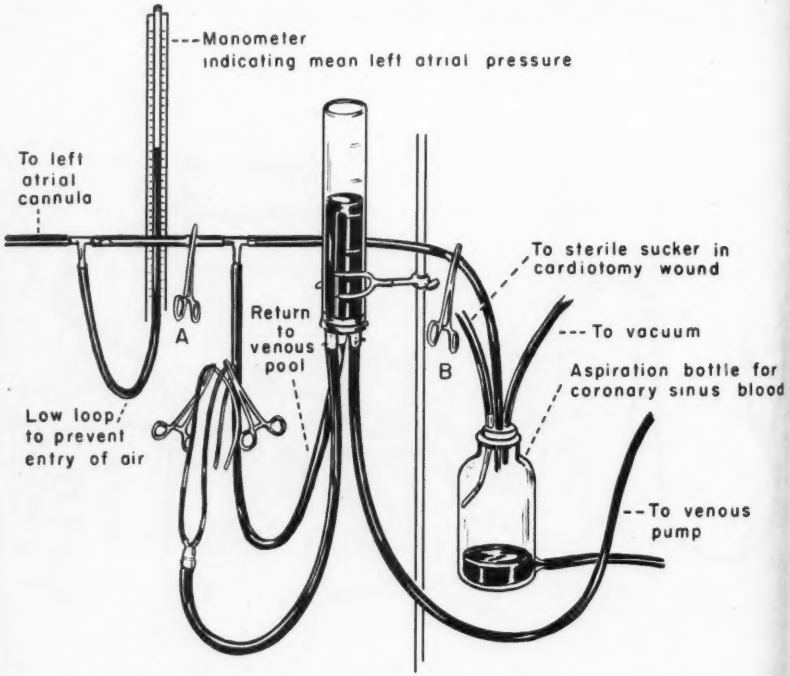

Fig. 5. Connections of left atrial cannula. Opening clamp A allows atrial blood to drain into the venous reservoir and hence back into the patient. If necessary, moving clamp A to the reservoir line and opening clamp B aspirates the cannula.

via the mechanical circulation with a minimum of handling. The manometer (vertical section) is used to ascertain whether the left atrial pressure is elevated. Elevation of that pressure may indicate that the patient should be maintained longer on the mechanical circulation.

It is important that the left atrial cannula not be exposed to negative pressure or to suction from the machine when the left heart is in any way open to the atmosphere, lest air be aspirated into the cavities of the heart.

Results

To date, the *device for automatic controls of the pump* has been used during 30 cardiotomies with total heart-lung bypass. After initial adjustments were made it worked smoothly. The efficiency of the device was proved recently when during a partial bypass the arterial outflow line became blocked: no changes in blood volume of the patient occurred. Before each run the controls are checked by raising and lowering the blood level in the oxygenator from a burette. With the use of a 9-inch oxygenator, a change of 75 ml. (1 mm. in height) of blood will operate all control lights; and with the 20-inch oxygenator, 125 ml. will do so. The automatic control can be switched to manual control instantaneously. In case of power failure, hand cranks can be snapped into the pump rotors within 10 seconds.

With the use of the open venous reservoir, the "vascular wall occlusion phenomenon" of the venous cannulae has not occurred. With the use of the left atrial cannula, increased pressure in the left atrium has been avoided, but the possibility of its occurrence during perfusions was proved by temporary (15 seconds) clamping of the outlet tube from the atrium to the venous reservoir.

Summary

Three devices are described to prevent overfilling of the pulmonary vascular bed and the disastrous pulmonary capillary damage that follows.

1. A device for automatic control of the blood volume of the Kay and Cross oxygenator consists of electrodes with a sensing voltage of 15 volts with no more than fifteen millionths of an ampere current. Volume changes of less than 125 ml. regulate the pumps.

2. An open venous reservoir, adjustable in siphon height, controls the venous outflow and prevents occlusion of the cannulae by the vascular walls being drawn into the tube openings.

3. A cannula in the left atrium monitors left atrial pressure, and through it blood may be released, if necessary, into the machine to avoid retrograde pulmonary overloading.

Erratum

In a previous paper[5] describing an electronic cardiac pacemaker and its use, reference to past significant work in this field by Hellerstein, Shaw, and Liebow[6] was omitted through an unfortunate oversight.

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EXECUTIVE'S DYSPHONIA

A Study of 49 Patients

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STRAIN and tension are widely recognized as affecting functions of the human nervous system. Communication by speech is a synthesis of functions whose finely balanced co-ordinations are easily disturbed by stimuli from the autonomic and sympathetic nervous systems. The business executive is exceptionally vulnerable to the development of functional vocal disorders. His work is accomplished by various means of oral communication—dictation, conferences, conversations by telephone—and strain and tension are inherent threats to his position of commanding or supervising other personnel, and even to his survival in today's highly competitive commercial enterprises.

It is the purpose of this paper to report the results of a study of 49 executives having functional vocal disorders (executive's dysphonia) and to report nonvocal symptoms that are present.

Selection of Patients

The records of 49 businessmen who had been referred for examination of the voice were selected on the basis of two criteria: (1) the patient held an executive position that involved command of and communication with a large number of persons, (2) his vocal disorder could be classed as functional dysphonia. Patients having contact ulcers or nodules in the larynx were included because these conditions are the result of abuse and misuse of the voice and generally can be treated without an operation.

Findings

The executives represented 12 main branches of business, a majority of which comprised sales and personnel, and included manufacturing, accounting, and engineering (Table 1). The ages of the patients ranged from 32 to 70 years, but 28 of the 49 patients were from 46 to 60 years of age (Table 2). Executives in this age group generally are regarded as being intellectually mature, as having sound judgment, and professionally as having arrived somewhere near the top of their fields of endeavor.

Some of the patients initially requested complete physical examinations, and because of the findings of vocal difficulties they were referred to the Department of Otolaryngology. However, most of the patients first reported their symptoms to the otolaryngologists and then were referred to other departments because of additional symptoms that possibly were closely related to the vocal problems.

Table 1. — *Types of business of 49 executives having dysphonia*

Executive field	Type of dysphonia, number of patients			
	Functional	Contact ulcers	Nodules	Total
Sales (not automobiles)	10	5	3	18
Manufacturing	4	1	1	6
Accounting	3	2	—	5
Engineering	3	2	—	5
Advertising	2	1	—	3
Construction	2	—	—	2
Purchasing	1	1	—	2
Utilities	1	1	—	2
Auto sales	2	—	—	2
Chain store supervision	2	—	—	2
Government	—	—	1	1
Union management	1	—	—	1
Total	31	13	5	49

Table 2. — *Age distribution of 49 executives having dysphonia*

Age, years	Type of dysphonia, number of patients			
	Functional	Contact ulcers	Nodules	Total
31-35	1	—	1	2
36-40	3	1	2	6
41-45	2	2	—	4
46-50	8	4	1	13
51-55	5	—	—	5
56-60	7	2	1	10
61-65	3	4	—	7
66-70	2	—	—	2
Total	31	13	5	49

The otolaryngologists reported 54 findings of diagnostic significance related to the nose, throat, and larynx in the 49 patients (Table 3). Forty-four of these findings were from the patients having functional dysphonia, six from the

Table 3.—*Findings of diagnostic significance in 49 executives having dysphonia*

Finding	Type of dysphonia, frequency of findings			
	Functional	Contact ulcers	Nodules	Total
Reported by Department of Otolaryngology				
Chronic rhinitis	17	6	2	25
Chronic laryngitis	10	—	2	12
Faulty vocal-cord action	7	—	—	7
Nervous tension, headaches	6	—	—	6
Carotid tenderness	4	—	—	4
Total	44	6	4	54
Reported by other departments				
Gastrointestinal disturbances	16	4	1	21
Anxiety tension state	13	4	2	19
Pains in chest and low back	7	2	—	9
Asthma (hay fever)	4	1	—	5
Chronic nervous exhaustion	4	—	—	4
Tension in neck and shoulders	2	1	1	4
Dizziness	2	—	—	2
Total	48	12	4	64
Total, all departments	92 (78%)	18 (15%)	8 (7%)	118 (100%)

patients having contact ulcers, and four from the patients having nodules. Chronic rhinitis was the single most frequent finding.

Physicians in other departments reported 64 findings of diagnostic significance (Table 3), 10 more than the number reported by the otolaryngologists. Forty-eight of the findings were from patients having functional dysphonia, 12 from those having contact ulcers, and four from those having nodules. The most frequent findings were gastrointestinal disturbance including gastric, peptic, or duodenal ulcers, and constipation, and anxiety tension state.

To summarize the medical findings: among the 49 executives there were 118 findings of diagnostic significance, or an average of more than two findings per patient. Although the patients having functional dysphonia comprised only 63 per cent of the entire group, their diagnostic findings comprised 78 per cent of the total.

Interviews and examinations by the vocal therapist produced still another large assortment of observations and diagnostic findings. The duration of the

vocal disorders ranged from one month to 20 years: in 14 patients for from one to three months; in 9 for six months; in 17 for one year; in 5 for from two to three years; in 1 for five years; and in 3 for twenty years.

The 49 patients reported 243 symptoms: 153 by those having functional dysphonia, 63 by those having contact ulcers, and 27 by those having nodules. Hoarseness was reported by all patients. In Table 4, the symptoms are listed according to frequency. A total of 194 vocal deviations such as hoarseness, monotony, and breathy voice was observed by the therapist, an average of four deviations per patient. The types of deviations are recorded in order of frequency in Table 5.

More than half of the 49 patients had limited ranges of speaking pitch (Table 6). An indication of their limitations is obtained from the comparison of their ranges with the range of intonation of a normal man's voice, which is about one and one-half octaves or 18 half tones; only 17 of the patients had a range of 16 or more half tones. A still more indicative observation was the level of pitch that each patient used in relation to the total range of his speaking voice. The man with a normal voice usually uses a level of pitch that is at the lower tone in the middle third, or the upper tone in the lower third of his total tonal range. This pitch is equal to six or eight half tones above the lowest tone in his total range. However, practically all of the executives spoke below their respective normal levels of pitch. In fact, 12 of them spoke at the lowest pitch of their tonal ranges, and 15 others, within a full tone above it. Only four of the executives may be said to have spoken at their normal levels of pitch.

Table 4.—*Symptoms reported by 49 executives having dysphonia*

Symptoms	Type of dysphonia, frequency of symptoms			
	Functional	Contact ulcers	Nodules	Total
Hoarseness	31	13	5	49
Vocal fatigue	24	7	1	32
Tension in neck, jaw, and lips	17	10	4	31
Throat cleared often	17	7	3	27
Sore muscles in neck	16	7	4	27
Voice better in morning	15	4	3	22
Throat dry, burning, sore	12	6	6	24
Voice better on Monday	8	3	—	11
Excess mucus	5	2	—	7
Globus	4	2	1	7
Shortness of breath	4	2	0	6
Total	153	63	27	243

Treatment

In addition to voice therapy that was recommended for all 49 patients, other forms of treatment were advised as indicated in Table 7. Voice therapy was directed toward the correction of the many symptoms that the patients reported or of the deviations that the therapist observed. Since the most outstanding problem was the low-pitched voice, efforts were primarily directed toward establishing the pitch of each patient's speaking voice at a level that would create clear phonation under conditions of the greatest efficiency of voice production. The patients having ulcers or nodules were given special attention in this respect. The patients having functional dysphonia had many correlated vocal problems that could be solved only by re-establishing what might be called *relaxed natural phonation.* In many patients this was effected only after concentrated training in proper breathing (usually diaphragmatic), in adequate air support, and in simple or basic phonation under conditions of physical relaxation which often were aided by external heat treatment.

Each patient was instructed in the mechanisms of voice production so that he could understand the mistakes he had been making and the process required for him to re-establish an adequate voice. He also was told that the correction of his vocal defect could best be accomplished through a series of guided-practice sessions. Thirty-seven of the patients accepted the offer of an individual training program and most of them had from one to three lessons in addition to the initial interview. The duration of the treatment ranged from one to nine months (Table 8).

Table 5.—*Vocal deviations in 49 executives having dysphonia*

Type of deviation	Type of dysphonia, frequency of deviation			
	Functional	Contact ulcers	Nodules	Total
Weak volume	31	9	4	44
Hoarseness	25	12	5	42
Pitch too low	24	13	2	39
Poor sense of pitch*	13	6	2	21
Monotonous voice	13	5	1	19
Gravel voice	6	—	—	6
Breathy voice	3	2	2	7
Huskiness	3	1	—	4
Voice breaks	2	5	4	11
Pitch too high	1	—	—	1
Total	121	53	20	194

**Patient could not reproduce a presented tone within one or two full tones.*

Table 6.—*Pitch of 45* executives having dysphonia*

Speaking pitch	Type of dysphonia, number of patients			
	Functional	Contact ulcers	Nodules	Total
Range—half tones (normal average range is 18 half tones)				
0-5	3	—	—	3
6-10	3	—	1	4
11-15	15	3	3	21
16-20	8	5	1	14
21-25	—	3	—	3
Total	29	11	5	45
Speaking pitch, half tones above lowest tone in range (6 half tones above lowest tone in range is normal)				
0 (same)	10	1	1	12
1	5	3	1	9
2	3	2	1	6
3	5	3	—	8
4	2	1	1	4
5	1	1	—	2
6	1	—	1	2
7	1	—	—	1
8	1	—	—	1
Total	29	11	5	45

**Four patients were not tested.*

Results of Voice Therapy

Voice therapy was successful in all of the 37 patients who participated in the training program: 31 achieved clear voices and 6 had improved voices (Table 8). In nine of the 10 patients having contact ulcers who received voice therapy, the ulcers disappeared or improved; and in all five of the patients having nodules, the nodules cleared or improved, as reported by the otolaryngologists. Patients have remained symptom-free in the follow-up period ranging from three months to four years. The three patients having contact ulcers who refused therapy remained unimproved; in one, an additional granulation developed and surgical treatment was necessary. Of the nine patients having functional dysphonia who did not receive voice therapy here, five refused the therapy and appeared to be satisfied with the results of tranquilizers; three

Table 7. — *Types of treatment advised for 49 executives having dysphonia*

Therapy advised	Type of dysphonia, number of patients			
	Functional	Contact ulcers	Nodules	Total
By otolaryngologists				
Antihistaminics or hypoallergenics	9	5	2	16
Diet and vitamins	7	5	4	16
No smoking	6	—	—	6
Prednisone	1	2	—	3
Tranquilizer	—	2	—	2
Total	23	14	6	43
By other physicians				
Tranquilizers, sedatives	9	5	2	16
Heat, massage, relaxation	8	4	—	12
Antihistaminics	2	—	—	2
Antispasmodics	—	1	3	4
Total	19	10	5	34
Grand total	42	24	11	77

refused the therapy because they were "too busy," and one was referred to another therapist.

Report of Four Typical Cases

Case 1. A 42-year-old man, an executive of a large corporation, reported vocal fatigue after talking at length or singing. The fatigue often was accompanied by a feeling, described by him as of "having my throat torn out" and of an obstruction and dryness in the throat. His voice was practically inaudible at the end of the working day. He shunned social events, to avoid talking, and he was desperately concerned about the possible failure of his voice at important sales meetings. Shortly before examination here the vocal symptoms had been unusually severe during and after a long, trying sales meeting. Although he had taken penicillin and nicotinic acid, prescribed by three local physicians, the vocal symptoms had not been relieved.

The otolaryngologic examination here revealed a chronic rhinitis, chronically irritated larynx, and excessive mucus that caused him to clear his throat frequently. The patient's voice was breathy, weak, husky, and unprojected. He had minimal labial and jaw action, his lips were held tensely in a straight line, and his larynx was pulled upward

Table 8.—*Data on 49 executives having dysphonia*

Therapy and status	Type of dysphonia, number of patients			
	Functional	Contact ulcers	Nodules	Total
Number of lessons				
Interview only	9	3	0	12
1 to 3	16	4	4	24
4 to 6	6	3	—	9
7 to 12	—	3	1	4
Total	31	13	5	49
Duration of therapy				
Interview only	9	3	—	12
1 month	9	5	3	17
2 months	11	3	2	16
3 to 5 months	2	1	—	3
8 months	—	1	—	1
Total	31	13	5	49
Status after therapy *				
Voice				
Clear	17	9	5	31
Improved	5	1	—	6
Larynx				
Clear	—	9	3	12
Improved	—	—	2	2

**Twelve did not receive voice therapy here (nine having functional dysphonia and three having contact ulcers).*

a full inch on simple phonation. The diagnosis was functional dysphonia. The gastroenterologists reported that he had an irritable colon.

The recommended treatment consisted of a hypoallergenic diet, an antihistaminic, Co-Pyronil (pyrrobutamine compound, Lilly), and voice therapy. Voice therapy was directed toward the development of adequate breath support through diaphragmatic breathing, relaxation of the muscles of the neck, face, and jaw, and a raise in pitch from G below low-C to low C. During the five lessons given during four months, the patient was entirely co-operative. Two weeks after therapy was begun his voice was greatly improved in clarity and the lump in his throat was gone; 10 weeks after therapy was begun his voice was practically normal, and one month later the dryness in his throat was gone and he was able to direct all conferences with a strong voice. Nine months after therapy was begun, the patient had no vocal symptoms; he had attended two conventions without having a vocal problem.

Case 2. A 45-year-old man, a sales executive, had been hawking frequently and coughing for two years because of increasing irritation in the throat. After a strenuous sales campaign he had pain on each side of the larynx. Three otolaryngologists treated the disorder with antibiotics, but a fourth otolaryngologist found a contact ulcer and referred the patient to our Department of Otolaryngology.

At initial examination here, the patient reported that he felt "something" in his throat, and that the pain that had been intermittent now was constant. He cleared his throat frequently and violently, and swallowed often. He occasionally had nausea, said he "felt whipped" at night and had to rub the muscles of his neck for relief. He had built up a fine business but now was almost constantly anxious both at work and at home.

The otolaryngologic diagnosis was contact ulcer on the right vocal cord process. The patient was advised to stop smoking at once, and to take voice therapy. Analysis of his voice indicated a low-pitched, weak but rough voice with flabby action of the vocal cord and inadequate breath support. Therapy was directed toward elevation of the pitch of his voice, development of a sustained tone, and elimination of the frequent nervous clearings of the throat. Methods of general relaxation were demonstrated to him in the Department of Physical Medicine. One week later, the patient was more relaxed; he had stopped clearing his throat; and his voice was clearer as well as higher in pitch. Two weeks after therapy was begun, his voice was clear, strong, and well projected. He had read aloud for two hours without fatigue, pain, huskiness, or tension, and was free from nausea and anxiety. Such extensive use of the voice is not recommended at such an early stage of therapy, but it demonstrates the patient's eagerness to rehabilitate himself. Within one month after the beginning of therapy, a healing membrane was observed over the ulcer. The patient was seen monthly for six months and had no recurrence of the lesion.

Case 3. A 59-year-old man, an executive mill accountant, had symptoms resembling those of a cold 18 months prior to examination here, which resulted in a whispering voice that had not completely recovered. He had been treated for laryngitis.

The patient had an extremely weak, breathy, half-aphonic trembling voice at a pitch higher than that of the average man. He appeared to be reluctant to talk for fear of losing his voice completely. The muscles of his neck bulged and his clavicle rose prominently during phonation. He reported that his throat ached and felt cramped after he had talked. Though he was short of breath he had adequate vital capacity. His "voice grew tired" before the end of the day and he dreaded meeting visitors in his office because of the additional talking it required.

The otolaryngologic diagnosis was tension dysphonia, and voice therapy was recommended. Three lessons in voice and two demonstrations of relaxation including the use of an infrared lamp were given within one month. At the time of the second lesson his voice had improved, but tension remained in the neck and the shoulders. One week later his phonation was steadier and the volume in his voice was greater. His acquaintances did not recognize his improved voice over the telephone. He continued to use the infrared lamp at home, and to practice sustaining his tone and increasing his volume. In spite of two emotionally upsetting personal crises, he maintained the gain in vocal power, and within one month after his first lesson he had a normal voice and was free from abnormal muscular tensions.

Case 4. A 48-year-old man, owner of a large business, and a part-time politician, had a voice disorder periodically for more than 10 years. The disorder had begun when he attended a convention where there was loud talking in a smoke-filled room. His voice became weak and raspy but subsequently returned to normal. At every succeeding convention he had the same experience, except that after the last convention he did not recover his voice. He was treated with oil spray in the throat and heat lamp to the

throat twice each week for one year by a local physician. Upon the advice of an otolaryngologist he rested his voice for three weeks; his voice improved, but the hoarseness returned when he resumed a normal amount of talking. He found that whenever he went fishing his voice improved!

At examination here, the diagnosis was bilateral nodules of the vocal cords. Voice therapy was prescribed. The voice therapist reported that the patient's voice was extremely rough, raspy, and low pitched, his breathing was clavicular, the lip movement was poor, and he cleared his throat frequently. Therapy was directed toward raising the pitch of his speaking voice two full tones and developing diaphragmatic breathing with adequate air support and with smooth, relaxed intonation. Three weeks after two lessons given two weeks apart, and practice at home, the patient attended a convention, and for the first time in 10 years returned home with a normal voice. Five weeks after beginning therapy, all symptoms of irritation in the throat had disappeared. Members of his club commented on the improvement in his voice. Laryngeal examination at the end of six months showed no evidence of the nodule. Four years later the patient still had a good voice despite his regular participation at conventions and his cheering at ball games.

Summary

A study was made of 49 executives having vocal disorders originating from misuse and abuse (functional dysphonia, contact ulcers, or nodules), executive's dysphonia. The otolaryngologists reported 54 findings of diagnostic significance, the most frequent of which were chronic rhinitis (in 25 patients) and chronic laryngitis (in 12); while specialists from other departments reported 64 findings of diagnostic significance, the most frequent of which were anxiety tension states or chronic nervous exhaustion (in 23), and gastrointestinal disorders (in 21). In addition, the 49 patients reported 243 symptoms, of which hoarseness was the most common, being mentioned by all. The duration of the vocal defects ranged from one month to 20 years. A total of 194 vocal deviations was observed by the therapist, an average of four deviations per patient.

Voice therapy was recommended for all 49 patients. Other forms of treatment also were advised, including antihistaminics, hypoallergenics, diet, vitamins, tranquilizers or sedatives, heat, massage, and general relaxation.

It is believed that best results are obtained from combined therapy consisting of voice lessons and medical measures. Treatment was successful in each of the 37 patients who accepted voice therapy; each one achieved a clear or an improved voice.

GROSS INTRAVENOUS EXTENSION OF CARCINOMA OF THE LUNG

A Preliminary Report

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THE search for findings of prognostic significance at the time of operation for neoplastic disease is a continuous one. One such finding is that of venous invasion by a malignant tumor. In specimens of cancer of the colon such a demonstration is limited to microscopic evidence, as the invaded veins are too small for gross dissection. Conversely, in specimens of renal carcinoma, the large size of the veins facilitates gross examination for neoplastic invasion. The veins in specimens of carcinoma of the lung also are of a size to permit gross examination, yet no record of such an examination has been found, although the possibility of carcinoma of the lung invading the veins has often been mentioned.

Initially, one of us (L. J. M.), while making a survey of the occurrence of neoplastic cells in blood draining from pulmonary neoplasms, noted a frequency of venous invasion by such tumors.[1] Although our case material is too recent for us to be able to make an adequate statistical evaluation in regard to survival of patients, we have sufficient pathologic data to report the immediate findings.

Material and Methods

Between January 1, 1953, and October 1, 1955, 345 patients with bronchogenic carcinoma were examined at the Cleveland Clinic. Some form of pulmonary resection was later performed in 79 of those patients, 48 of whom underwent pneumonectomy and 31 of whom were treated with lobectomy.

The unfixed surgical specimens were examined using a technic different from the usual pathologic procedure. Instead of initially opening the bronchi to expose the neoplasm, the major pulmonary veins first were longitudinally opened. The surgeon had left long ligatures on the veins to facilitate their positive identification. This was necessary, as carcinoma of the lung occasionally also invades the large pulmonary arteries, as had occurred in two of the 79 specimens in this series. After the veins were opened they were carefully

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searched for a protruding thrombus (Fig. 1). This evidence of neoplastic invasion was noted in the region of the tumor, often recurring at points of union of the smaller venous tributaries. Those specimens showing only narrowing of the lumen of a vein by impingement of extraluminal tumor were not included in the group considered to be positively invaded.

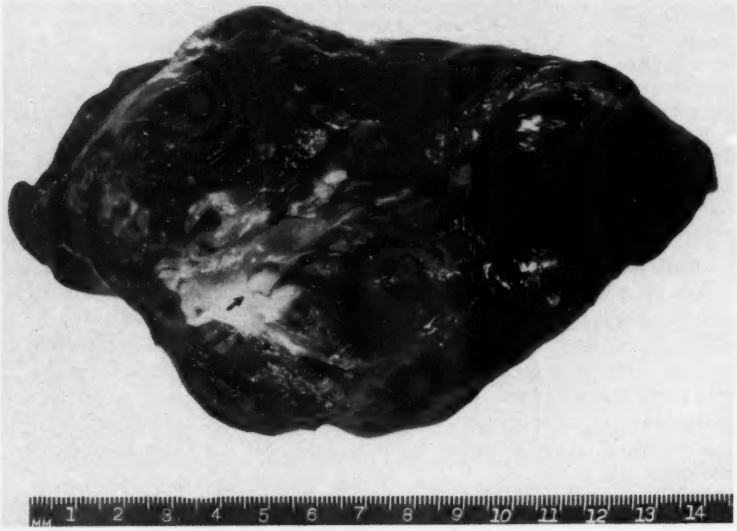

Fig. 1. Gross neoplastic invasion of pulmonary vein. The pulmonary vein has been opened longitudinally to show the protuberant mass (arrow).

The size of the intravascular neoplasm ranged from a mass 0.3 cm. long to one that completely occluded the major vein and extended into the left atrium. A microscopic section of every neoplastic thrombus was made to establish positively whether the tumor had or had not actually invaded the venous wall and formed the intravascular mass (Fig. 2).

Findings

Demonstrable gross intravascular extension was present in the surgical specimens of 19 of the 79 patients. Seventeen of these patients were available for survival studies; one patient died in the early postoperative period and one patient was lost to follow-up. The cell types of neoplasm in this group were squamous-cell carcinoma, 12 specimens; adenocarcinoma, two specimens; and undifferentiated carcinoma, three specimens. An associated hilar lymph-node involvement was present in seven patients. Postoperatively, eight of the 17 patients were still living and well for periods of from 17 to 48 months; the others

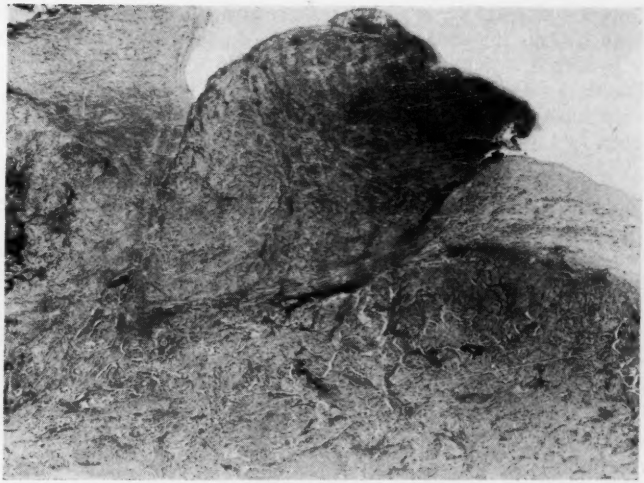

Fig. 2. Photomicrograph showing mass of neoplasm protruding into lumen of vein. Hematoxylin-eosin and methylene blue stain; x 9.

had died. A postoperative follow-up of three or more years was possible for 10 of these 17 patients. Only two of these 10 patients survived for three or more years; one of these survivors had intravenous extension en masse into the left atrium.

The surgical specimens of 60 patients showed no evidence of gross intravenous extension; 53 of these patients were followed, as six died in the immediately postoperative period and one was lost to follow-up. The neoplastic cell types in this group were squamous-cell carcinoma, 23 specimens; adenocarcinoma, 20 specimens; undifferentiated carcinoma, eight specimens; and small-cell carcinoma, two specimens. There was an associated lymph-node involvement in 30 of the 53 patients. Of the 53 patients, 23 were living and well for periods from 17 to 49 months after operation; 14 of the 22 survived three or more years postoperatively. This is in contrast to two of 10 patients so surviving who had intravenous extension of tumor.

Although the series at this time is too limited for statistical evaluation, it may be noted that among the 17 patients with squamous-cell carcinoma traced three years or more, six of nine having no gross intravenous extension survived in comparison with two of eight who had venous neoplastic invasion.

Summary

1. Evidence of gross intravenous extension was found on pathologic examination of 19 of 79 surgically resected specimens of carcinoma of the lung.

2. Only two of 10 patients with intravenous extension survived three years or more in contrast to 14 surviving among 22 patients without such venous invasion by tumor.

3. The data suggest that in the absence of gross neoplastic invasion of the pulmonary veins, the survival rate is higher than when such invasion is demonstrable.

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DIET AND HYPERCHOLESTEREMIA

A Comment

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CONCERN with the amount of serum cholesterol, its relation to dietary fat and to cholesterol, and the association of hypercholesteremia with atherogenesis is widespread. It is reflected in the divergent opinions expressed both in scientific and in lay journals and in the recent report[1] of a Joint Commitee of the American Heart Association and the American Society for the Study of Arteriosclerosis. The latter report reviews primarily the problem of a diet that is good for the general population. It suggests that from 25 to 30 per cent of calories be obtained from fat, with the further provision that the fat be sufficient "to meet caloric and essential fatty acid demands." Most physicians are less concerned with diets for general consumption than with diets for their individual patients who have definite elevations of serum cholesterol concentration (more than 300 mg. per 100 ml. as determined by most methods) and also may present family or personal histories either of xanthoma or of premature arteriosclerosis or of both diseases. The purpose of this paper is to summarize present-day dietary approaches to the control of hypercholesteremia.

Two dietary programs are currently employed. One is the strictly low-fat diet and the other is a diet containing a minimum of animal fat along with sufficient vegetable oil to provide a normal *total* fat intake. These two distinctly different approaches, unfortunately, are sometimes misinterpreted as being interchangeable. Misunderstanding may be fostered by commercial advertisements that seem to lead one to believe that control can be established simply by taking vegetable oil, as a medication, with the implication that the oil is substantially noncaloric.

The low-cholesterol diet can be dismissed from separate consideration because such a diet is intrinsically low in animal fat. Furthermore, the ingestion of cholesterol without fat has no appreciable effect on the concentration of serum cholesterol.

Fats and Serum Cholesterol

The various kinds of fat are distinguished, in part, by the amounts of iodine that they can absorb; these values are a convenient measure of saturation or hydrogenation and are known as "iodine values." Animal fats, the popular hydrogenated shortenings and tropical nut oils such as coconut oil or cocoa butter, are relatively highly saturated and have low iodine values. Commercially available vegetable oils contain a large proportion of unsaturated fatty acids,

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primarily linoleic, and have high iodine values. Some of the unsaturated fatty acids are required for the proper nutrition of rats and other mammals. Because they are not synthesized by the organism, and must be supplied in the diet, they often are referred to as "essential fatty acids."

The saturation of an individual fat determines the effect on serum cholesterol when the fat is taken by human beings as the only source of dietary fat. Saturated fats, such as those present in dairy products—meats, eggs, margarines and hydrogenated shortenings—tend to increase the amount of serum cholesterol; relatively unsaturated vegetable oils tend to decrease the amount of serum cholesterol. When saturated and unsaturated fats occur together in the diet, the hypercholesteremic tendency of each gram of saturated fat can be counteracted by about 3 gm. of unsaturated fat. These facts have been determined by special "formula" diets[2,3]. Valuable as they are in tests, such formula diets are unpalatable and impractical for common use.

The Normal Diet

The normal American food pattern or diet provides 47 per cent of total calories as carbohydrate, 12 per cent as protein and 41 per cent as fat.[4] In relation to a daily intake of 2,000 calories, this diet means 235 gm. of carbohydrate, 60 gm. of protein and 90 gm. of fat. Such a diet contains per day the following basic food stuff: two servings of meat, 1 pint of milk, 1 egg, 6 slices of bread with butter or margarine, a cereal, fruit, a vegetable, and a dessert. One fifth of the fat comes from dairy products; one third from table fat (butter or margarine) and cooking fat (lard or commercial shortening); one third from meat; and the rest from eggs, fruits, cereals, and vegetables.[5] In this normal diet, 85 per cent of the fat is saturated and 15 per cent is unsaturated (Fig. 1).

The Low-Fat Diet

The low-fat diet *omits* as much of all fats as possible from all food sources. It provides only from 10 to 15 per cent of the total calories as fat. These calories are obtained by eating from 30 to 40 gm. of fat daily, from 15 to 30 gm. of which is relatively saturated animal fat. In effect, the low-fat diet reduces the saturated-fat intake to an amount that does not affect the concentration of serum cholesterol. The low-fat diet eliminates fat-containing dairy products, table and cooking fats, egg yolks, and nuts. Intake of meat fat is reduced by avoiding pork and by using instead lean beef, and by frequent use of veal, poultry, and fish. A 2,000-calorie daily diet, then, would be comprised of 360 gm. of carbohydrate, from 60 to 70 gm. of protein, and 30 gm. of fat.

The low-fat diet we use includes 30 gm. of fat daily (Fig. 1). This is mostly saturated fat and substantially all of it is eaten at *one* meal. The reason for this "one fat meal" is that metabolism of ingested fat given at frequent intervals, may be delayed, and favors accumulation of the fat in the serum.[6] Moreover, by con-

centrating the day's fat in one meal, the patient is assured of having one satisfying meal a day, and is more likely to follow the diet. This regimen can be followed at home or at work with little difficulty.

The Vegetable-Oil Diet

This diet *substitutes* vegetable oil for most of the fat that would be eaten in a normal diet. In the vegetable-oil diet, as in a normal diet, about 40 per cent of the calories is derived from fat; from 5 to 10 per cent of the calories comes from animal fats, and from 30 to 35 per cent from unsaturated vegetable oils. As with the low-fat diet, the consumption of animal fat is restricted to from 15 to 20 gm. daily, but there also is provided from 60 to 100 gm. of vegetable oil (Fig. 1). The intake of carbohydrate and of protein corresponds to that of a normal diet.

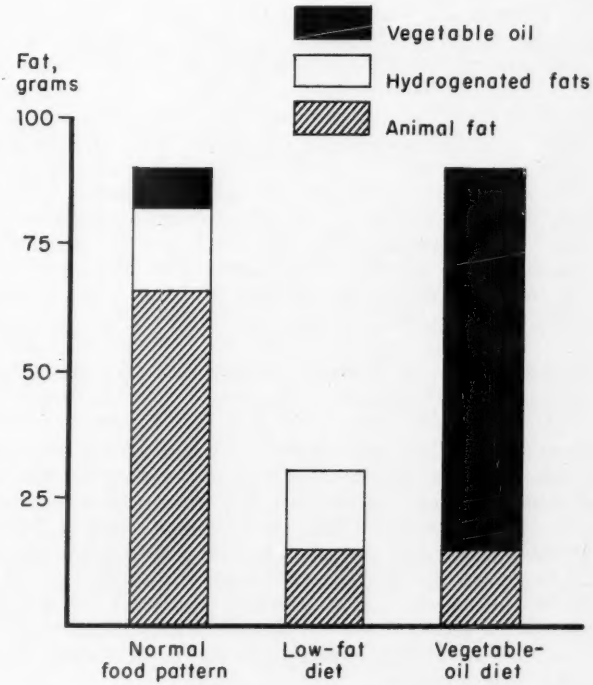

Fig. 1. Chart showing amounts and kinds of fat in normal, low-fat, and vegetable-oil 2,000-calorie diets.

The vegetable-oil diet is basically a low-fat diet with the addition of vegetable oils, such as corn, soya, peanut, or cottonseed oil. It is effective in decreasing the amount of serum cholesterol, because it curtails intake of saturated animal fats below the hypercholesteremic concentration, and increases the intake of unsaturated vegetable oil to the extent that it exerts a hypocholesteremic effect. The diet is prepared by substituting an unsaturated vegetable oil for the meat, dairy, and table fats of the normal diet.

It is important to recognize that this regimen requires the *substitution* of one kind of fat for another. The *addition* of a few tablespoons or capsules of vegetable oil, however prepared, to a basically normal food pattern will not alter the proportion of saturated to unsaturated fats sufficiently to affect the amount of serum cholesterol.[7] It would take almost a pint of vegetable oil each day to counteract the effect of the usual amount of dietary saturated fat contained in the normal diet. A sufficient intake of one of the unsaturated oil preparations can depress the amount of serum cholesterol in persons who simultaneously restrict their intake of animal fat. The calories supplied by the oils used medicinally necessarily supplant calories obtained from food; this means that a large portion of appetizing food is sacrificed.

Because it seemed to us that a vegetable oil regimen can be successful in practice—if it is practical and acceptable, closely corresponds to a normal American food pattern, provides a flexible diet, and can be readily prepared from easily available foods—we have undertaken a study of vegetable-oil diets in which these oils are used as food rather than as medication. Among the oils under study is a preparation of cottonseed oil.* This modified cottonseed oil can be made into a spread for bread, can be used as shortening in baked goods, and will emulsify in a blender with nonfat milk solids to yield reconstituted "milk," "cream," or "ice cream" of any desired fat content.

The clinical part of the study has been conducted in collaboration with Harriet P. Dustan, M.D., and Roland E. Schneckloth, M.D., over periods of from three to 18 months, in 30 patients with hypercholesteremia and hyperlipemia, several of whom have xanthomatosis and some of whom have myocardial infarcts. It has also involved short-term, carefully controlled tests in seven normal persons and 18 of the above-mentioned patients. Many of the patients had followed low-fat diets for from three to 15 months before changing to the vegetable-oil diets.

Preliminary results will be reported in detail elsewhere, but, briefly, we have found that both the low-fat (one fat meal daily) and the vegetable-oil diets can reduce and maintain concentration of serum cholesterol at amounts less than those prevailing during periods of free dietary intake. Either of the diets may decrease the amount of serum cholesterol to within acceptable limits. When a maximum reduction seems to have resulted from the low-fat diet, the addition of vegetable oil often causes a further decrease (Fig. 2). A few patients whose serum lipid patterns represent severe "essential" hypercholesteremia (rather than mixed, presumably familial hyperlipemia and hypercholesteremia) do not respond well to either regimen.

Prepared under the supervision of Fred H. Mattson, Ph.D., Research and Development Department, Procter & Gamble Company, Cincinnati, Ohio.

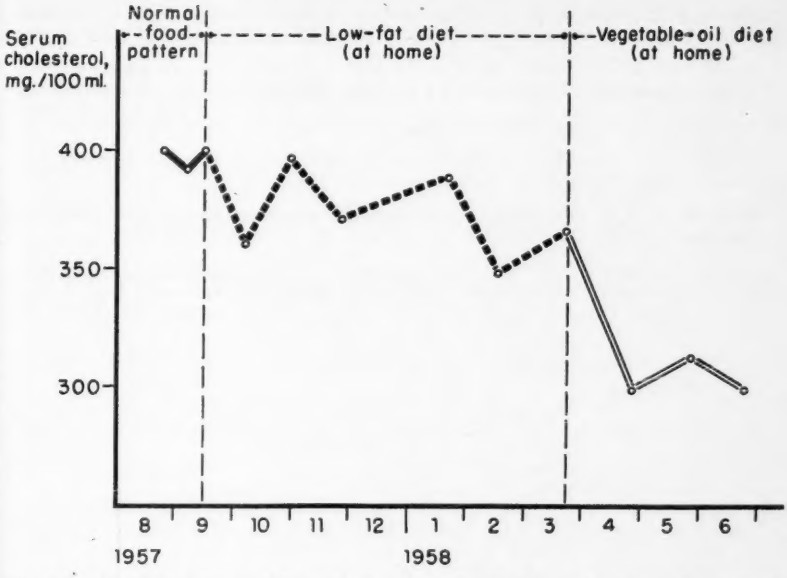

Fig. 2. Graph showing serum cholesterol values in a hypercholesteremic patient who received normal, low-fat, and vegetable-oil diets successively from August, 1957, into June, 1958.

Summary

1. The normal, the low-fat, and the vegetable-oil diets are compared in regard to the amount and the nature of the fat content and the effect on serum cholesterol in hypercholesteremia.

2. The low-fat diet may depress the amount of serum cholesterol by the severe restriction of intake of saturated animal fat. The diet is easily followed when most of the daily fat intake occurs at one meal.

3. The vegetable-oil diet (in which vegetable oils are substituted for most of the animal fat in a normal diet) may cause depression of the amount of serum cholesterol below the lowest limit attained with a low-fat diet. This effect is attributable to the hypocholesteremic effect of unsaturated fat.

4. Attention is directed to the undesirability of regimens in which vegetable oils are used as medications only, or are added to diets in which animal fat is not restricted.

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